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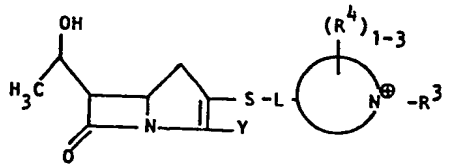
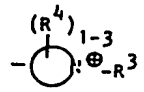
(54) **Carbapenems having an externally alkylated mono- or bicyclic 2-quaternary heteroarylalkylthio substituent.**

(57) Carbapenems having the formula:



wherein



is a mono- or bicyclic quaternary heteroaryl, their preparation and antibiotic use are disclosed.

EP 0 167 139 A1

-2- 16330IFY

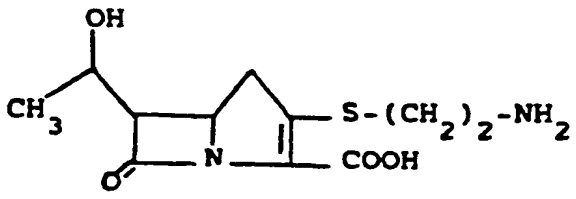
TITLE OF THE INVENTION

CARBAPENEMS HAVING AN EXTERNALLY ALKYLATED MONO- OR BICYCLIC 2-QUATERNARY HETEROARYLALKYLTHIO SUBSTITUENT

BACKGROUND OF THE INVENTION

The present invention is concerned with carbapenems antibiotics having a quaternary mono- or bicyclic heteroaryl containing group in the 2-position.

Thienamycin is a known carbapenem, broad spectrum antibiotic of the formula:



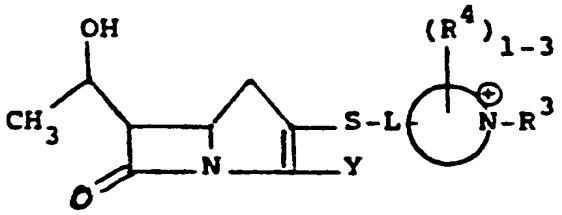
A

Other derivatives of A are also known.

The present externally alkylated mono- or bicyclic 2-quaternary heteroarylalkylthio substituted carbapenems have an antibiotic spectrum equal to or better than A. The present carbapenems also are more resistant than A to degradation by the dehydropeptidase enzyme DHP-I.

SUMMARY OF THE INVENTION

Carbapenems having the formula:



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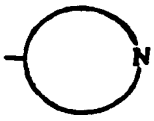
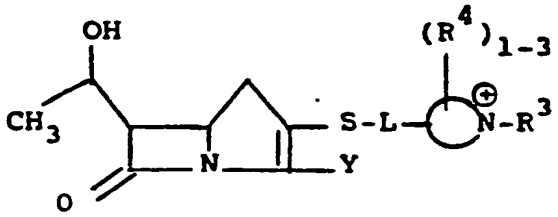
wherein R^3 is a quaternizing substitutent, R^4 is a ring hydrogen or substituent, L is a covalent bond or a bridging group,  is mono- or bicyclic heteroaryl, and

Y is a carboxy containing substituent.

DETAILED DESCRIPTION OF THE INVENTION

The invention is embodied in a compound having the formula:



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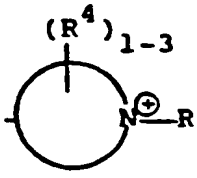
wherein:

L is a covalent bond or a bridging group selected from $-(CH_2)_{1-4}S-$; $-(CH_2)_{1-4}-O-$; $-(CH_2)_{1-4}-X-(CH_2)_{1-4}$ where X=O, S, NH, or $N(C_1-C_6)$alkyl; substituted or unsubstituted C_1-C_4 straight, C_1-C_6 branched or C_3-C_7 cycloalkyl groups wherein the substituents are selected from C_1-C_6 alkyl, $O-C_1-C_6$ alkyl, $S-C_1-C_6$ alkyl, halo, OH, CF_3, CN, NH_2, NHC_1-C_6 alkyl, $N(C_1-C_6$ alkyl$)_2$, CO_2H, $CONH_2$, $CONH(C_1-C_6$ alkyl), and $CON(C_1-C_6$ alkyl$)_2$;



R^3 is a mono- or bicyclic heteroarylium group containing from 5-11 ring atoms of which up to 5 are heteroatoms wherein R^3 is:

1) an unsubstituted or substituted C_1-C_6 alkyl radical;
2) an unsubstituted or substituted C_1-C_6 alkenyl radical;

3) an unsubstituted or substituted C_1-C_6 alkynyl radical;

4) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;

5) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;

6) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;

7) an unsubstituted or substituted bivalent C_2-C_6 alkylidene radical, optionally interrupted by a heteroatom, and joined to the heteroarylium group to form a ring which is carbocyclic or in which one or more atoms is replaced by a heteroatom. The new ring may contain one or more double bonds;

8) an unsubstituted or substituted phenyl or heteroaryl radical;

9) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical;

10) a cyano (C_1-C_4 alkyl) radical;

11) a carbamoyl (C_1-C_4 alkyl) radical;

12) a hydroxy (C_1-C_4 alkyl) radical;

13) an amino (C_1-C_4 alkyl) radical in which the nitrogen atom is unsubstituted or substituted with one to three C_1-C_4 alkyl groups;

14) an acidic side-chain of the structure

$-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

n = 0-4

m = 0-4

X = CHR^s, CH=CH, phenylene ($-C_6H_4-$), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;

R^s = H, O(C1-C4 alkyl), NH_2, NH(C1-C4 alkyl), N(C1-C4 alkyl)$_2$, CN, $CONH_2$, CON(C1-C4 alkyl)$_2$, CO_2H, SO_2NH_2, SO_2NH(C1-C4 alkyl);

Y = single bond, NH, N(C1-C4 alkyl), O, S;

A = an acidic function such as carboxy (CO_2H), phosphono [$P{=}O(OH)_2$], alkylphosphono {$P{=}O(OH)$-[$C(C_1$-C_4 alkyl)]}, alkylphosphinyl [$P{=}O(OH)$-(C_1-C_4 alkyl)], substituted phosphoramido [$P{=}O(OH)NH(C_1$-C_4 alkyl) and $P{=}O(OH)NHR^X$], sulfino (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H), arylsulfonamido (SO_2NHR^X) and acylsulfonamides represented by the structures $CONHSO_2(C_1$-C_4 alkyl), $CONHSO_2N(C_1$-C_4alkyl)$_2$ - $SO_2NHCO(C_1$-C_4 alkyl) and SO_2NHCOR^X;

R^X = aryl or heteroaryl as defined above;

wherein the substituents in the above definitions of R^3 are independently selected from the group consisting of the definitions of R^4 set out below:

R^4 is independently selected from:

a) a trifluoromethyl group;

b) a halogen atom;

c) an unsubstituted or substituted C_1-C_4 alkoxyl radical;

d) a hydroxy group;

e) an unsubstituted or substituted (C_1-C_6 alkyl) carbonyloxy radical;

f) a carbamoyloxy radical which is unsubstituted or substituted on nitrogen with one or two C_1-C_4 alkyl groups;

g) a C_1-C_6 alkylthio radical, C_1-C_6 alkylsulfinyl radical or C_1-C_6 alkylsulfonyl radical, each of which is unsubstituted or substituted on the alkyl group;

h) a sulfamoyl group which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;

i) an amino group;

j) a mono (C_1-C_4 alkyl) amino or di(C_1-C_4 alkyl)amino group, each of which is unsubstituted or substituted on the alkyl group;

k) a formylamino group;

l) an unsubstituted or substituted (C_1-C_6 alkyl)carbonylamino radical;

m) a (C_1-C_4 alkoxyl) carbonylamino radical;

n) a ureido group in which the terminal nitrogen is unsubstituted or substituted with one or two C_1-C_4 alkyl groups;

o) a (C_1-C_6 alkyl)sulfonamido group;

p) a cyano group;

q) a formyl or acetalized formyl radical;

r) an unsubstituted or substituted (C_1-C_6 alkyl)carbonyl radical wherein the carbonyl is free or acetalized;

s) an unsubstituted or substituted phenylcarbonyl or heteroarylcarbonyl radical;

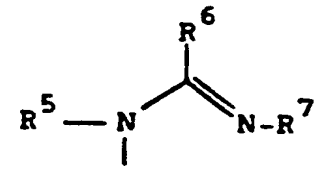
t) a hydroximinomethyl radical in which the oxygen or carbon atom is optionally substituted by a C_1-C_4 alkyl group;

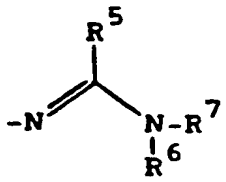
u) a (C_1-C_6 alkoxy)carbonyl radical;

v) a carbamoyl radical which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;

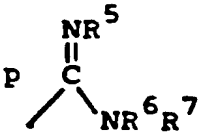
w) an N-hydroxycarbamoyl or N(C_1-C_4 alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C_1-C_4 alkyl group;

x) a thiocarbamoyl group;

y) an amidino group 



where R^5, R^6 and R^7 are independently hydrogen, C_1-C_4alkyl or wherein two of the alkyl groups together form a C_2-C_6alkylidene radical optionally interrupted by a heteroatom and joined together to form a ring;

z) a carboxamidino group  , where R^5, R^6 and R^7 are as defined above;

aa) a guanidinyl group where R^6 in ab) above is NR^8R^9 and R^8 and R^9 are as defined for R^5 through R^7 above.

ab) hydrogen;

ac) an unsubstituted or substituted C_1-C_6 alkyl radical;

ad) an unsubstituted or substituted C_1-C_6 alkenyl radical;

ae) an unsubstituted or substituted C_1-C_6 alkynyl radical;

af) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;

ag) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;

ah) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;

ai) an unsubstituted or substituted phenyl or heteroaryl radical;

aj) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical; and

ak) an acidic side-chain of the structure

-A or $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

n = 0-4

m = 0-4

X = CHR^s, CH=CH, phenylene ($-C_6H_4-$), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;

R^s = H, O(C1-C4 alkyl), NH_2, NH(C1-C4 alkyl), $N(C1-C4\ alkyl)_2$, CN, $CONH_2$, $CON(C1-C4\ alkyl)_2$, CO_2H, SO_2NH_2, $SO_2NH(C1-C4\ alkyl)$;

Y = single bond, NH, N(C1-C4 alkyl), O, S;

A = an acidic function such as carboxy (CO_2H), phosphono [$P=O(OH)_2$], alkylphosphono {$P=O(OH)-[C(C_1-C_4\ alkyl)]$}, alkylphosphinyl [$P=O(OH)-(C_1-C_4\ alkyl)$], substituted phosphoramido [$P=O(OH)NH(C_1-C_4\ alkyl)$ and $P=O(OH)NHR^X$], sulfino (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H), arylsulfonamido (SO_2NHR^X) and acylsulfonamides represented by the structures $CONHSO_2(C_1-C_4\ alkyl)$, $CONHSO_2N(C_1-C_4 alkyl)_2$ - $SO_2NHCO(C_1-C_4\ alkyl)$ and SO_2NHCOR^X;

R^X = aryl or heteroaryl as defined above;

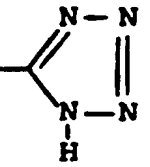
Y is selected from: i) COOH or a pharmaceutically acceptable ester or salt thereof, ii) $COOR^1$ wherein R^1 is a removable carboxy protecting group, iii) COOM wherein M is an alkali metal, or iv) $COO^{\ominus}$; provided that when Y is other than iv) a counterion $Z^{\ominus}$ is provided.

As used herein, the term "heteroatom" means nitrogen, oxygen, or sulfur, independently selected where more than one heteroatom is involved.

Representative L groups are $-CH_2-$, $-CH(CH_3)-$, $-CH(C_2H_5)-$, $-(CH_2)_{2-4}$, $-CH(CH_3)-CH_2-$, $CH_2-CH(OCH_3)-$, $-CH(CH_3)-(CH_2)_2-$, $-CH(CH_2OH)-CH_2-$, $-CH(CF_3)-CH_2-$, $-CH_2-CH_2-S$, $-CH_2-CH_2-O$, $-(CH_2)_2-S-CH_2-$, $-(CH_2)_2-O-CH_2$, a single covalent bond, and the like.

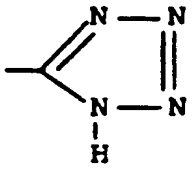
A preferred L group is a substituted or unsubstituted C_1-C_6 linear or branched chain alkyl. A more preferred L group is $-CH_2-$, $-CH(CH_3)-$ or $(CH_2)_2-$.

Examples of useful R^3 groups are $-CH_3$, $-(CH_2)_{1-3}-CH_3$,  , $-(CH_2)_{1-3}-O-CH_3$, $-CH_2-CN$, $CH_2-COOC_1-C_3$ alkyl, $-(CH_2)_2-N(C_1-C_3$ alkyl$)_2$.

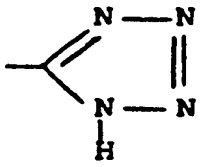
$-CH_2-COOH$, $-(CH_2)_2-SO_3H$,  .

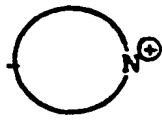
$-(CH_2)_2-\overset{\oplus}{N}(CH_3)_3$ and the like.

Preferred R^3 groups are the C_1-C_6 alkyls, both substituted and unsubstituted.

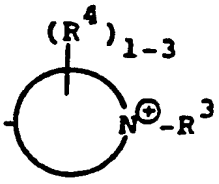
Preferred substituents are CN, $CON(CH_3)_2$, $CONH_2$, $SOCH_3$, SO_2CH_3, CO_2H, SO_3H, SO_2NH_2 and 

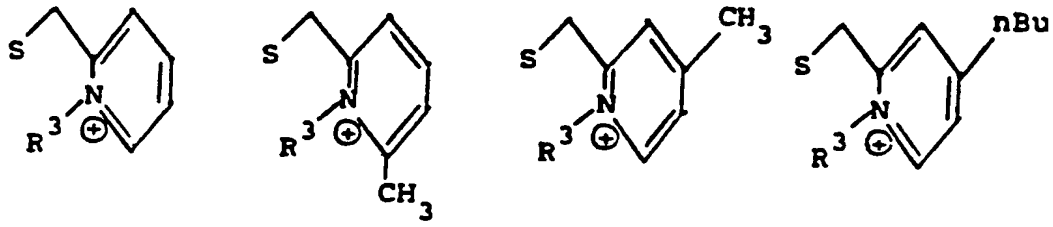
Examples of useful R^4 groups are OH, NH_2, $N(C_1$-C_3alkyl), OC_1-C_4alkyl, C_1-C_4alkyl, CN, CF_3, CH_2OH and the like.

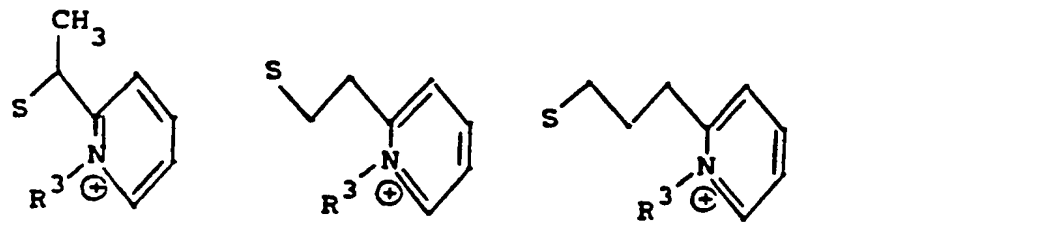
Preferred R^4 groups are CO_2H, CH_2CO_2H, SO_3H, CH_2SO_3H, $CONH_2$, CH_2CONH_2, CN, CH_2CN, SO_2NH_2  , $CH_2P(O)(OCH_3)(HO)$ and the like.

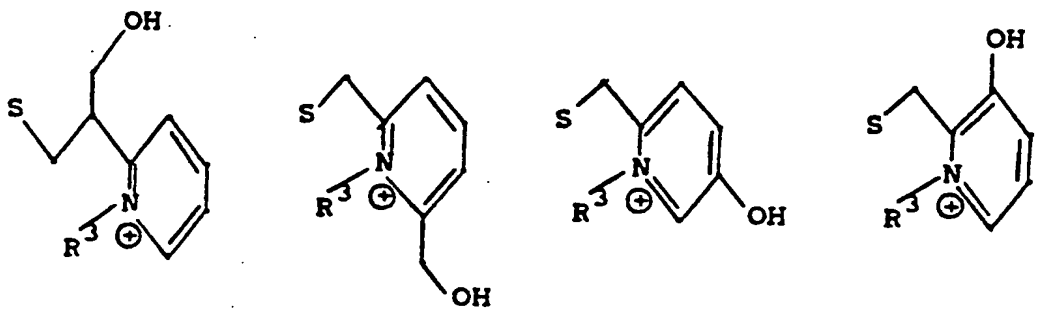
The  moiety is mono- or bicyclic quaternary heteroaryl group having 5-11 ring atoms of which, in addition to the quaternary $N^{\oplus}$, up to four can be heteroatoms.

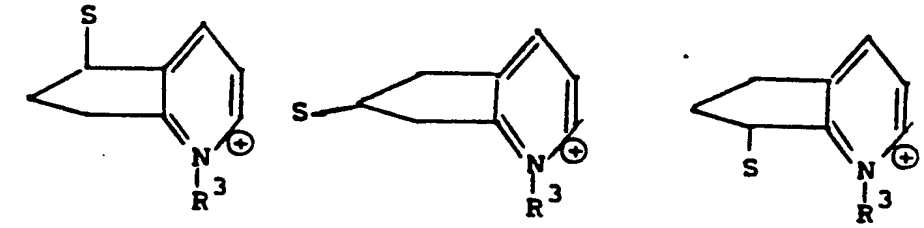
Of particular interest and the most preferred group are compounds of the present invention wherein the substituent on the N-containing mono- or bicyclic quaternary heteroaryl group in the 2-position is an acidic function as defined above and the Y substituent in the 3-position is $COO^{\ominus}$ as defined above, thus forming a zwitterion with the positive charge of the quaternary nitrogen. The acidic function is anionic and the compounds are thus anionic zwitterions, i.e., they have a net negative charge. This novel characteristic has been found to result in at least one surprising and important improvement in the biological properties of the compounds reduced CNS side-effects. A more particular group of the compounds, those wherein the acidic function is a sulfoalkyl group of the formula $(C_{1-4}$ alkyl$)SO_3^{\ominus}$, have been found to have the additional surprising and important biological property of enhanced potency against Pseudomonas species, an especially important nosocomial pathogen. In this most preferred group of compounds, it is preferred that the N-containing mono- or bicyclic quaternary heteroaryl group in the 2-position is pyridinium.

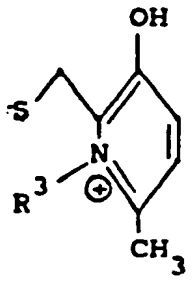
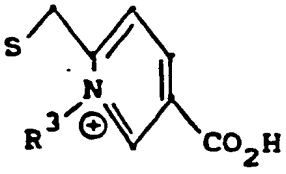
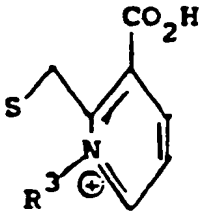
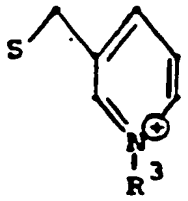
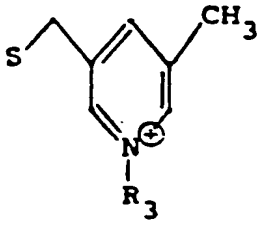
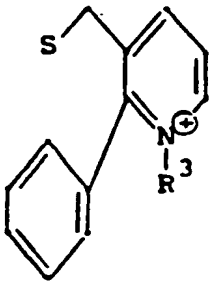
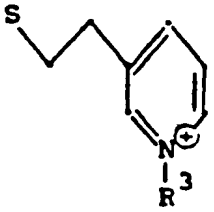
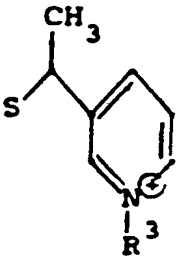
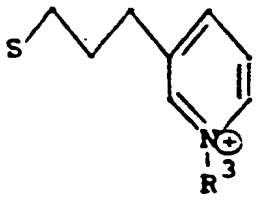
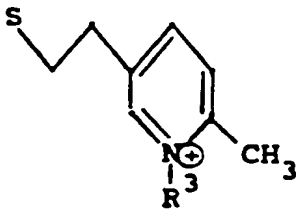
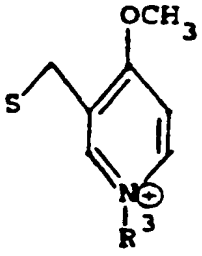
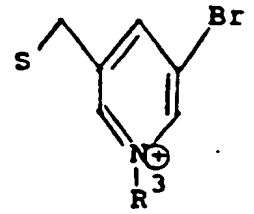
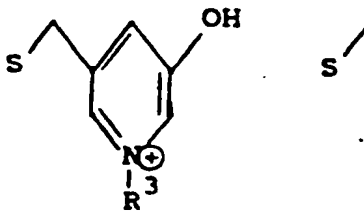
Examples of useful -S-L-  groups are:









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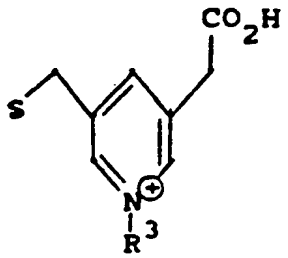
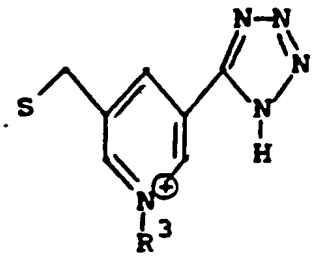
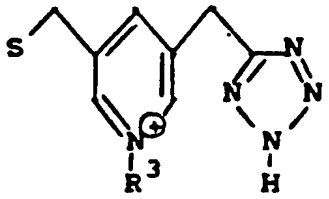
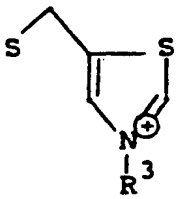
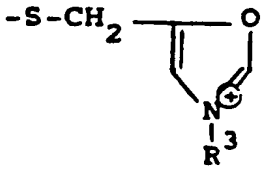
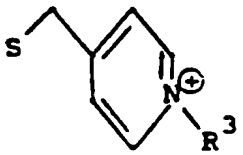


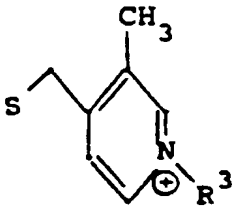


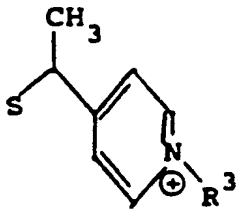


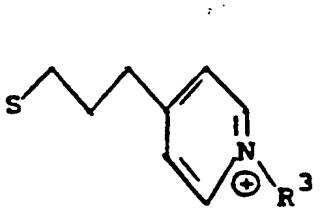


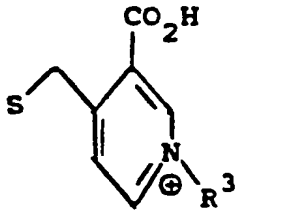


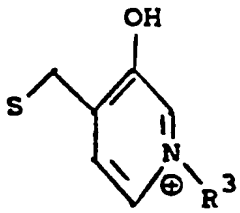


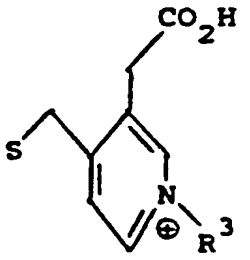


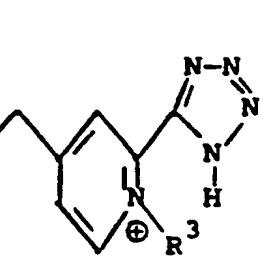


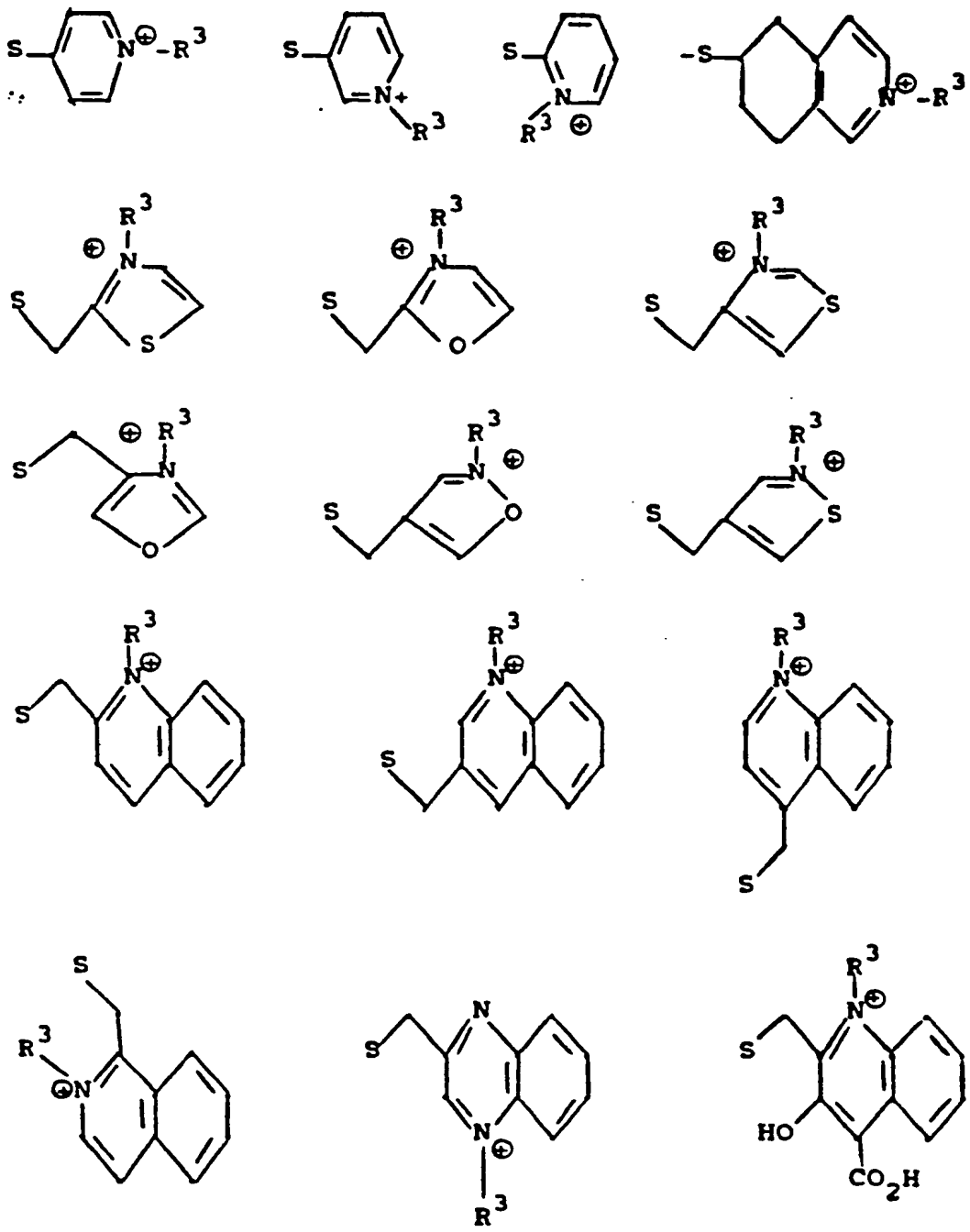


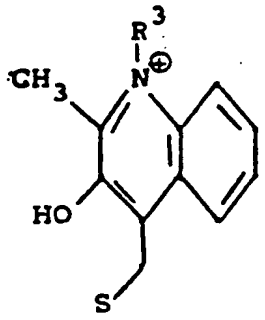


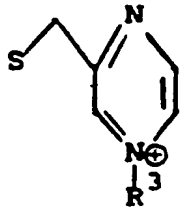


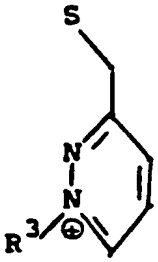


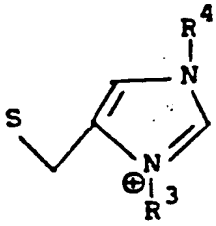


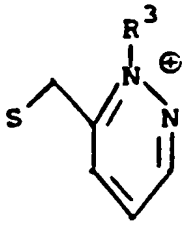


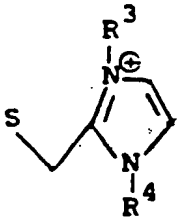


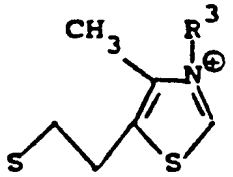


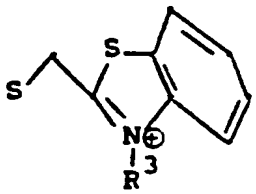


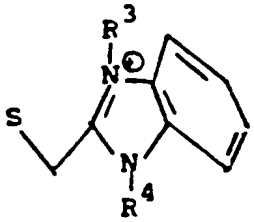


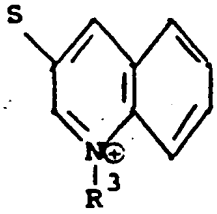


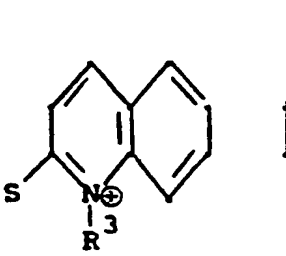


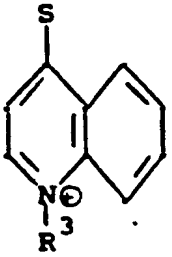


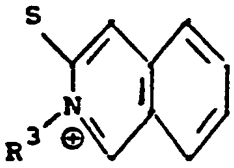


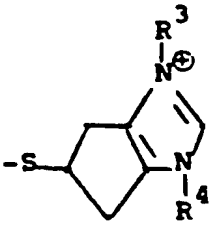


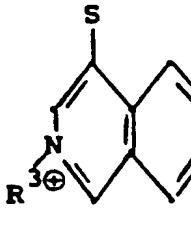


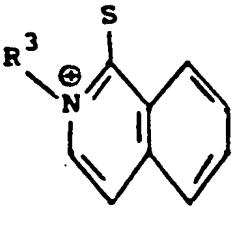


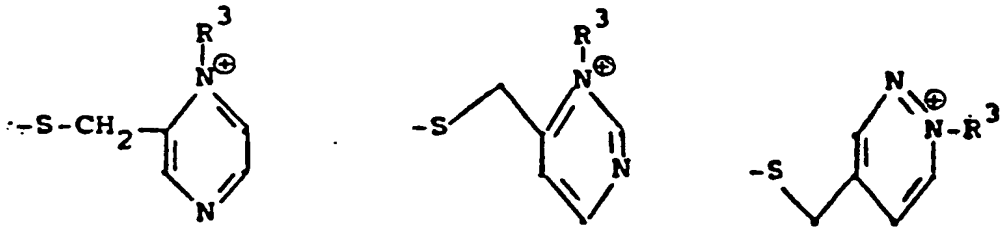


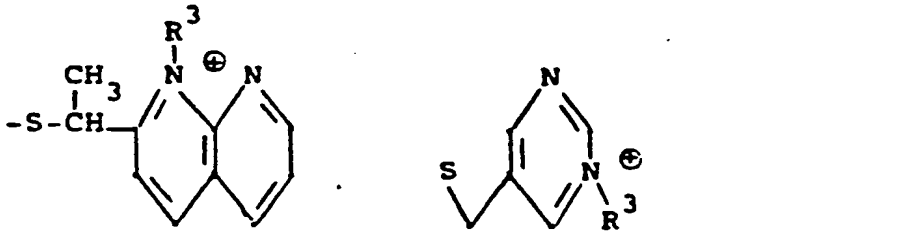


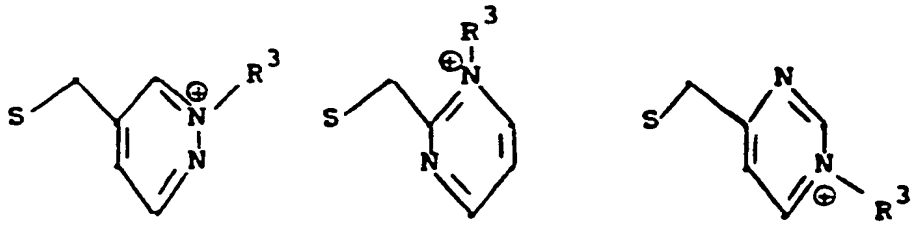


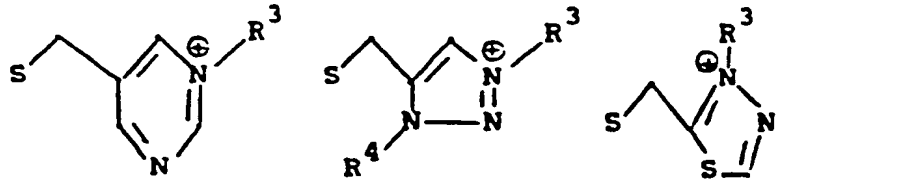


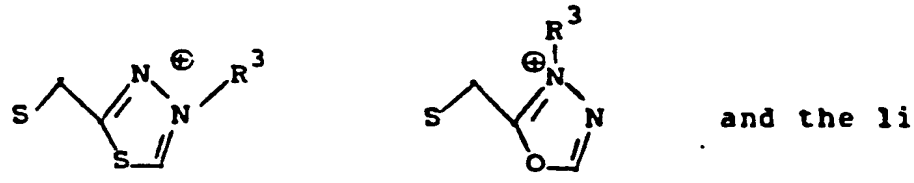




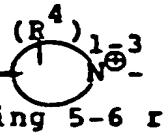


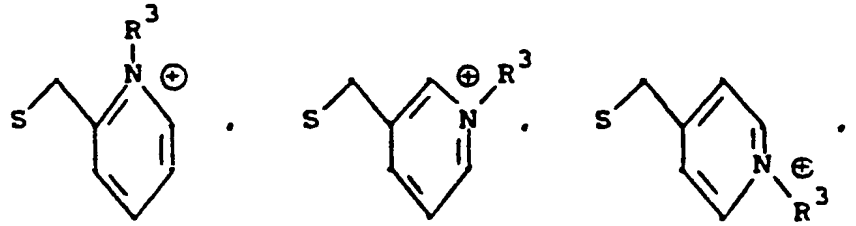


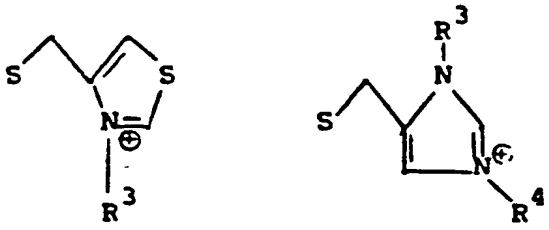
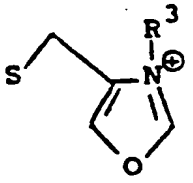




and the like.

A preferred S-L-  R^3 group is monocyclic heteroaryl having 5-6 ring atoms and optionally one heteroatom additional to the N atom already present, e.g.,

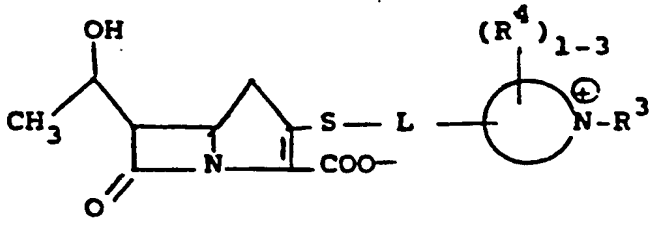


 and 

where R^3 and R^4 are as defined in the preferred list above.

A more preferred subclass includes the nuclei shown above where R^3 is CH_3 and R^4 is CH_3.

The compounds of Formula I include inner (Zwitterion) salts when Y is $COO^{\ominus}$ e.g.

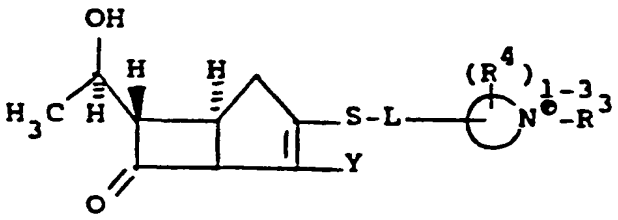


or, when Y is other than $COO^{\ominus}$, salts with an external, physiologically acceptable counterion $Z^{\ominus}$ such as $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, $OCH_3^{\ominus}$, $OSO_2CF_3^-$, $OP(O)(O\ phenyl)_2^{\ominus}$ and the like.

The inner salts are preferred.

Again, the compounds of Formula I include the stereoisomers as mixtures and as separate isomers.

A preferred isomer configuration is:



Ia

The compounds of the present invention (I) are valuable antibiotics active against various Gram-positive and Gram-negative bacteria and accordingly find utility in human and veterinary medicine. Representative pathogens which are sensitive to antibiotics I include: Staphylococcus aureus, Escherichia coli, Klebsiella Pneumoniae, Bacillus subtilis, Salmonella typhosa, Pseudomonas and Bacterium proteus. The antibacterials of the invention are not limited to utility as medicaments; they may be used in all manner of industry, for example: additives to animal feed, preservation of food, disinfectants, and in other industrial systems where control of bacterial growth is desired. For example, they may be employed in aqueous compositions in concentrations ranging from 0.1 to 100 parts of

antibiotic per million parts of solution in order to destroy or inhibit the growth of harmful bacteria on medical and dental equipment and as bactericides in industrial applications, for example in waterbased paints and in the white water of paper mills to inhibit the growth of harmful bacteria.

The compounds of this invention may be used in any of a variety of pharmaceutical preparations. They may be employed in capsule, powder form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically or parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents. Alternatively, the active ingredient may be in powder form for reconstitution, at the time of delivery, with a suitable vehicle, such as sterile water. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints, or powders.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated as well as the route and frequency of administration -- the parenteral route by injection being preferred for generalized infections. Such matters, however, are left to the routine discretion of the therapist according to

principles of treatment well known in the antibiotic art. In general, a daily dosage consists of from about 5 to about 600 mg of active ingredient per kg of body weight of the subject in one or more treatments per day. A preferred daily dosage for adult humans lies in the range of from about 10 to 240 mg of active ingredient per kg of body weight. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the chosen species of this invention (I).

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from 0.1% to 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 1500 mg of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 250 mg to 1000 mg. In parenteral administration, the unit dosage is usually the pure compound I in sterile water solution or in the form of a soluble powder intended for solution.

The preferred method of administration of the formula I antibiotic is parenteral by i.v. infusion, i.v. bolus, or i.m. injection.

For adults, 5-50 mg of Formula I antibiotic per kg of body weight given 2, 3, or 4 times per day is preferred. Preferred dosage is 250 mg to 1000 mg of the Formula I antibiotic given two (b.i.d.) three (t.i.d.) or four (q.i.d.) times per day. More specifically, for mild infections, and particularly

urinary tract infections, a dose of 250 mg t.i.d. or q.i.d. is recommended. For moderate infections against highly susceptible gram positive and gram negative organisms, a dose of 500 mg t.i.d. or q.i.d. is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of 1000 t.i.d. or q.i.d. is recommended.

For children, a dose of 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg t.i.d. or q.i.d. is usually recommended.

Antibiotic compounds of Formula I are of the broad class known as carbapenems or 1-carbadethiapenems. Certain of these carbapenems are susceptible to attack by a renal enzyme known as dehydropeptidase (DHP). This attack or degradation may reduce the efficacy of the carbapenem antibiotic. Inhibitors of DHP and their use with carbapenem antibiotics are disclosed in the prior art [see published European Patent Applications No. 79102615.6, filed July 24, 1979 (application no. 15573) and No. 82107174.3, filed August 9, 1980 (application no. 72014)].

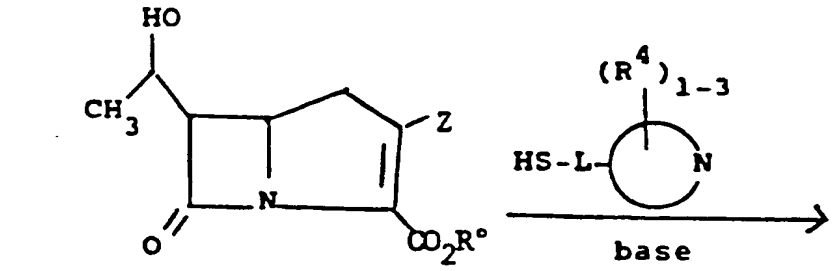
The present I compounds may, where DHP inhibition is desired or necessary, be combined or used with the appropriate DHP inhibitor as described in the aforesaid published applications. Thus, to the extent that the cited European patent applications 1.) define the procedure for determining DHP susceptibility of the present carbapenems and 2.)

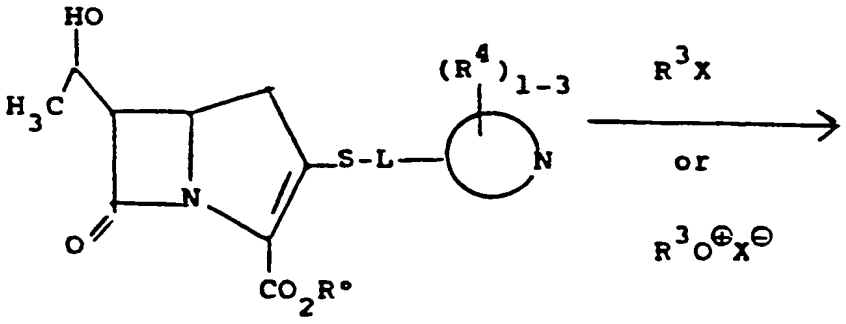
disclose suitable inhibitors, combination compositions and methods of treatment, they are incorporated herein by reference. A preferred weight ratio of I compound:DHP inhibitor in the combination compositions is about 1:1. A preferred DHP inhibitor is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid or a useful salt thereof.

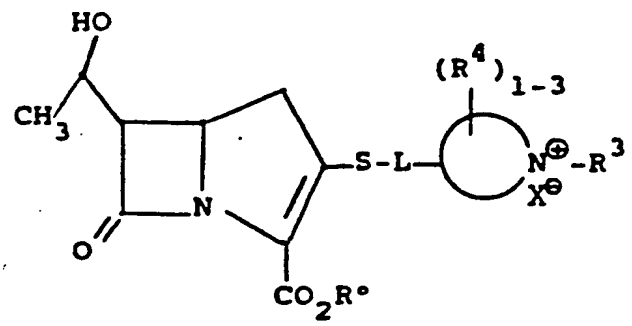
These combination compositions and their use is another embodiment of the present invention.

The compounds of Formula I may be prepared by any convenient process.

A. One such process is illustrated in the following reaction equations:

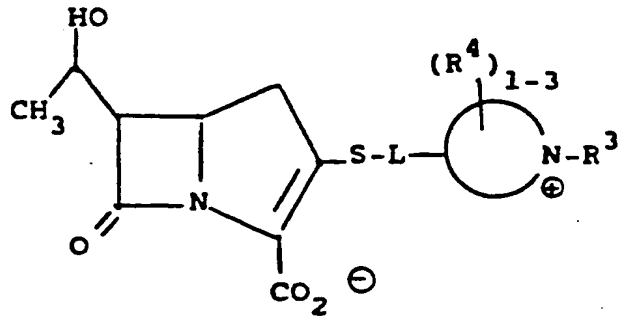






deblock

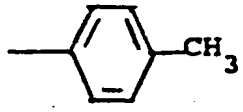
(remove R°)



I

wherein Z is a leaving group such as $-OPO(O\phi)_2$,

, OSO_2CF_3

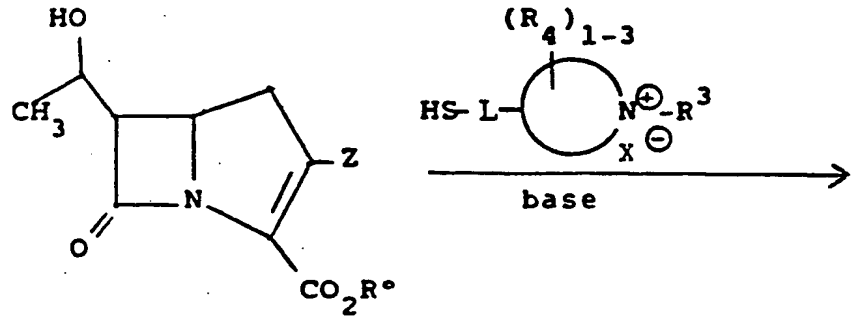
and the like, X is a leaving group such as Br, I, OSO_2CF_3, $-OSO_2F$, 

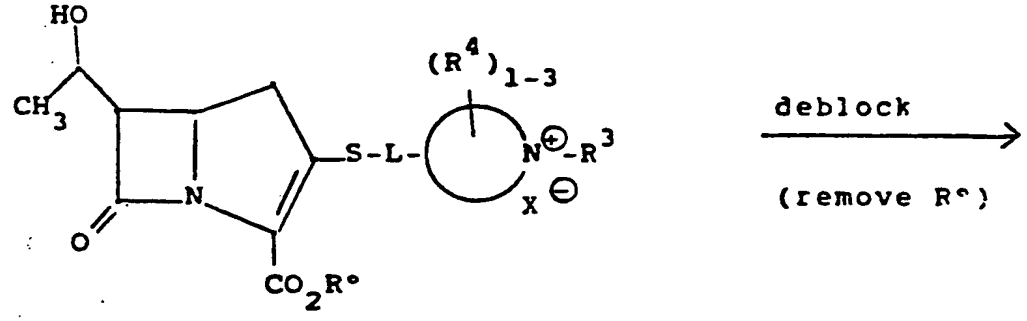
or X is an anionic group such as BF_4, SbF_5, PF_6 and the like; and R° is a protecting group such as p-nitrobenzyl or allyl. R^3, L and R^4 are as defined above.

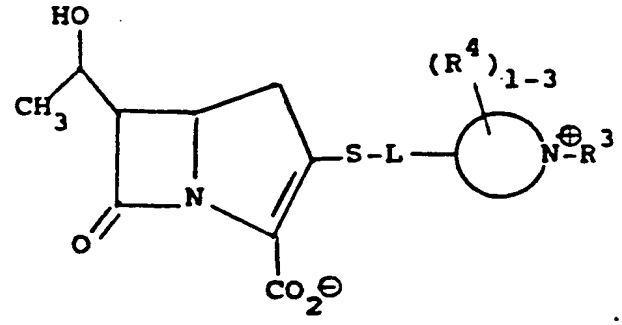
The side chain addition reaction is carried out in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide or N-ethyl-pyrrolidinone in the presence of a base such as

N,N-diisopropylethylamine, triethylamine or 4-dimethylaminopyridine at a temperature of from -40°C to 25°C for a period of five minutes to ten hours. The alkylation reaction is conducted in a solvent such as dichloromethane, dimethylformamide, acetonitrile or dimethylacetamide at a temperature of from -20°C to 25°C for a period of 1 to 24 hours. The deblocking reaction wherein R° is p-nitrobenzyl is usually conducted in an aqueous system containing cosolvents such as tetrahydrofuran, ethanol, n-butanol, i-amyl alcohol, or ethyl acetate and a pH 6.8 to 7.0 aqueous buffer. Suitable buffers include phosphate buffers and buffers derived from non-nucleophilic amines such as N-methylmorpholine or morpholinopropane sulfonic acid. The reaction is conducted at 0°C to 40°C for 0.5 to 5 hours under 1-100 atmospheres of hydrogen in the presence of a catalyst such as 10% palladium on carbon or 20% palladium hydroxide on carbon. The final products are purified by ion exchange chromatography and/or reverse phase chromatography. When a pharmaceutically acceptable ester of the final product is desired, the deblocking step is omitted and the appropriate R° group is incorporated into the starting material.

B. A second process is illustrated by the following set of equations:



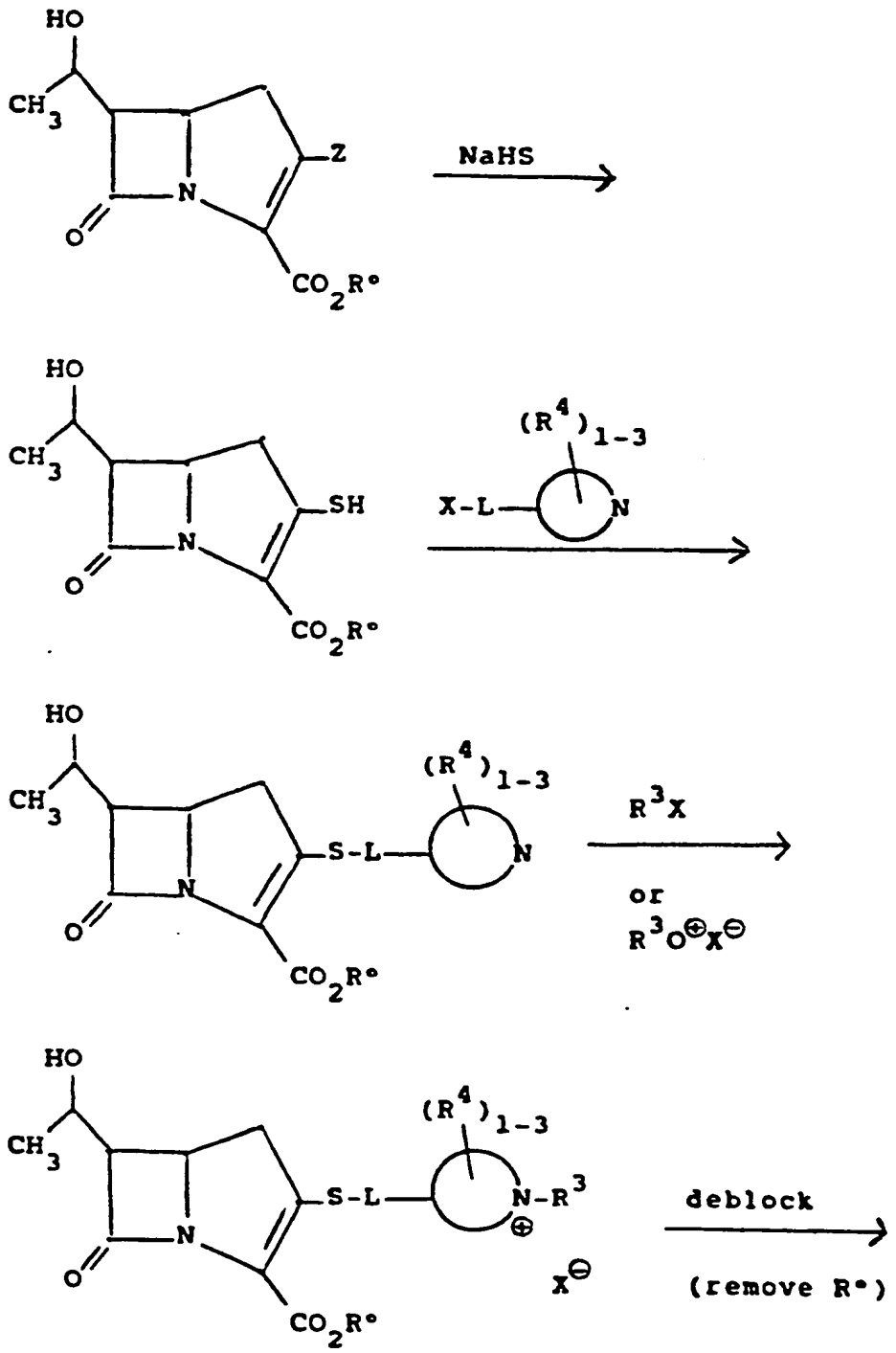


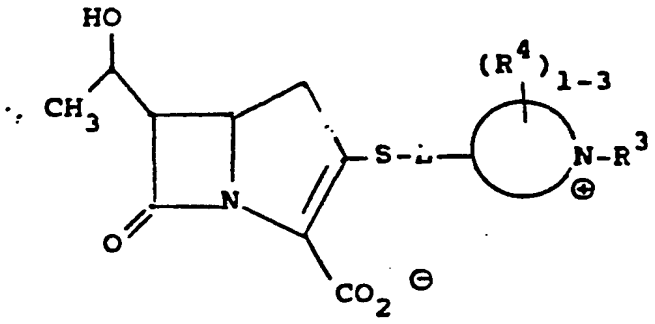


wherein Z, X, L, R°, R^3 and and R^4 are as defined above.

The difference between the above process and that earlier described is that the side chain moiety is alkylated with the group R^3 prior to addition to the carbapenem nucleus. The side chain addition step and deblocking are conducted as described above.

C. A third process is illustrated by the following set of equations:



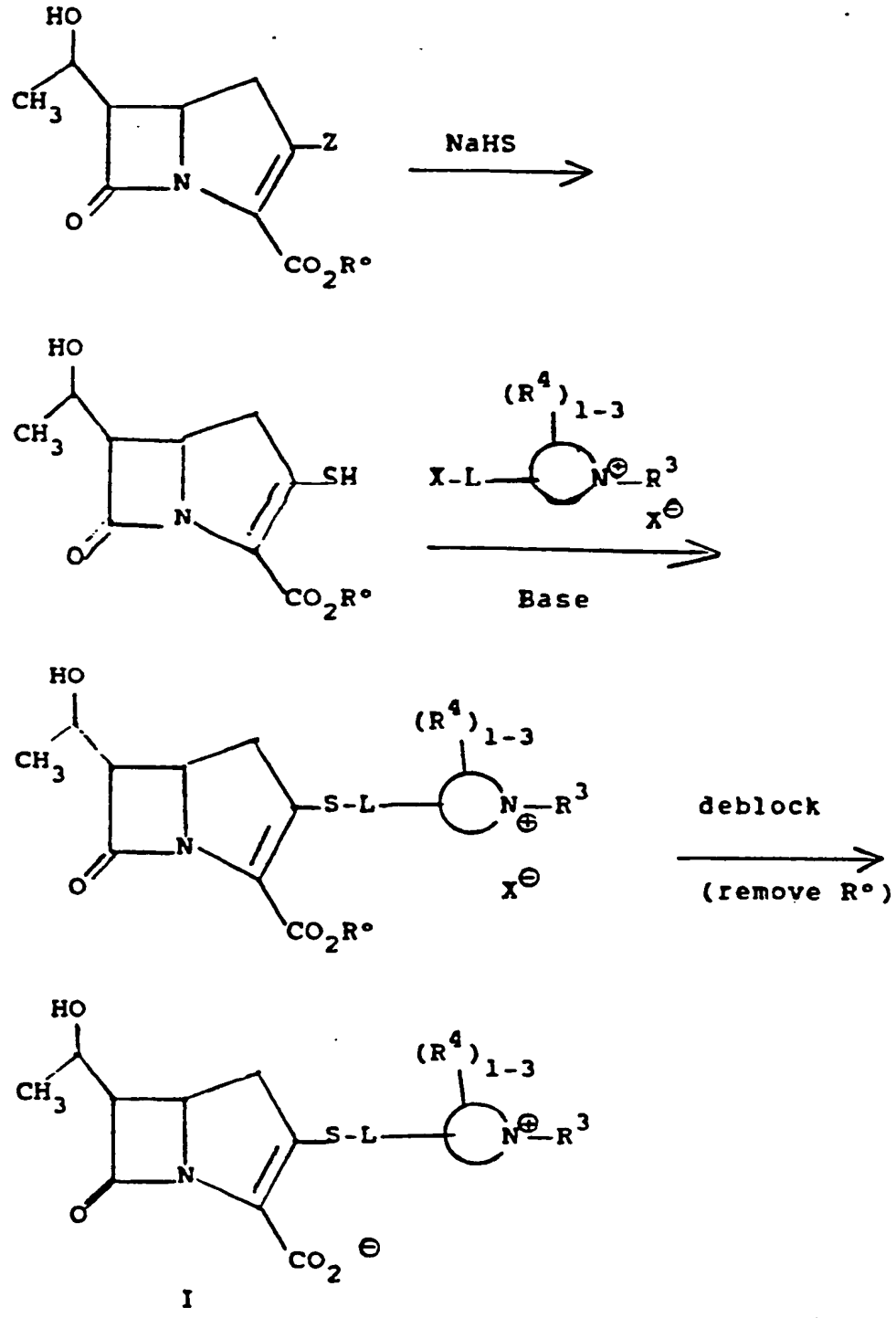


I

wherein Z, X, L, R°, R^3 and R^4 are as previously defined.

In this case the 2-mercapto intermediate is generated from the activated carbapenem upon exposure to sodium hydrosulfide in dimethylformamide or dimethylacetamide at a temperature of from -50°C to -20°C for a period of five minutes to one hour. The sulfur atom is alkylated in a solvent such as acetonitrile, dimethylformamide, dimethylacetamide or the like in the presence of a base such as N,N-diisopropylethylamine, triethylamine, 4-dimethylaminopyridine or the like at a temperature of from -40°C to 25°C for a period of from ten minutes to eight hours. The side chain alkylation, removal of R° and purification of I is conducted as described above.

D. A fourth process is illustrated by the following set of equations:



I

wherein Z, X, R°, R^3, and R^4 are as previously defined.

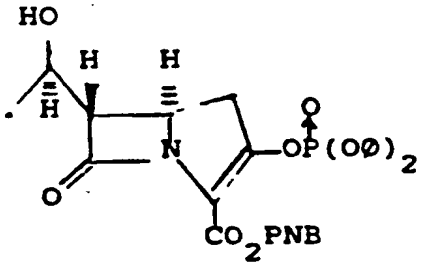
The difference between this process and that described in process C is that the side chain moiety is alkylated with the group R^3 prior to addition to the carbapenem nucleus. The side chain addition step and the deblocking are conducted as described above.

The following examples illustrate the preparation of compounds of Formula I. The temperature is in degrees Celsius unless otherwise indicated.

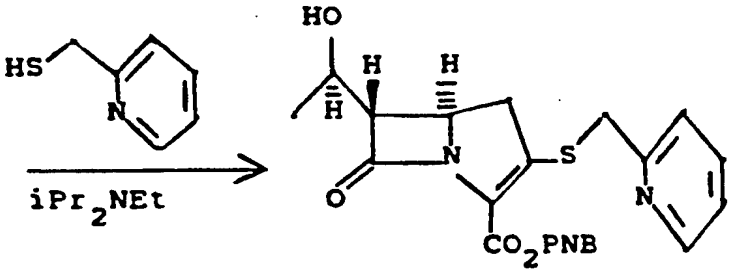
EXAMPLE 1

Step A.

Preparation of p-Nitrobenzyl (5R,6S)-6-(1(R)-hydroxyethyl)-2-(2-pyridylmethylthio)-carbapen-2-em-3-carboxylate 2.



1



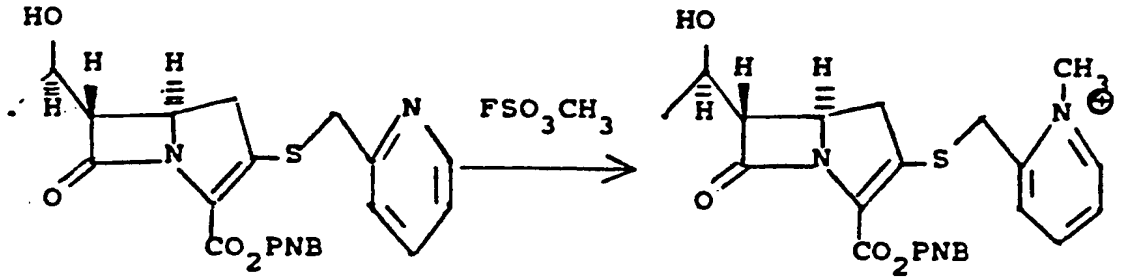
2

A solution of vinyl phosphate 1 (2.32 g, 4 mmoles) in anhydrous acetonitrile is cooled to -20° (ice-methanol) under a nitrogen atmosphere and treated with 2-mercaptomethylpyridine (0.554 ml, 5.0 mmoles) and diisopropylethylamine (0.871 ml, 5.0 mmoles). The resulting mixture is stirred at -20 to -15° for 60 minutes during which time a precipitate formed. The mixture is diluted with ethyl acetate (16 ml) and aged at -15° to -5° for 30 minutes. The precipitate is collected, washed with ice-cold ethyl acetate and dried *in vacuo* to give the product (1.095 g) as a white solid.

The filtrate and washings are diluted with ethyl acetate, washed with 0.1M pH 7 phosphate buffer two times and brine, dried over magnesium sulfate, filtered and concentrated to a semisolid. This material is triturated with ethyl acetate and ether two times and dried *in vacuo* to yield an additional 0.498 g of product. Total yield of 2 is 1.593 g, 87%.

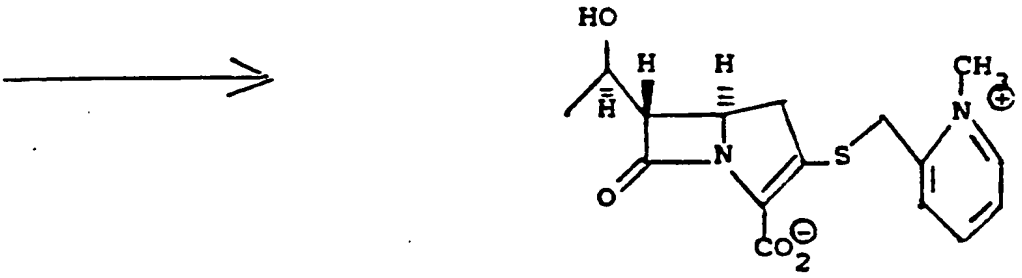
Step B.

(Preparation of (5R,6S)-6-(1(R)-hydroxyethyl)-2-(1-methyl-2-pyridinium)methylthio-carbapen-2-em-3-carboxylate 4.



2 3

H_2
Pd



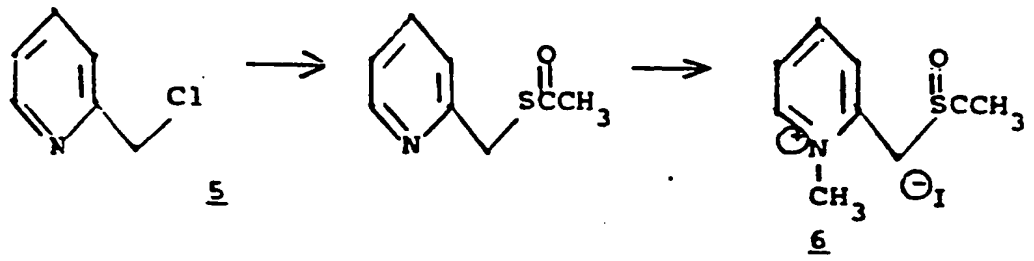
4

To a magnetically stirred solution of 2 (0.853 g, 1.87 mmole) in 15.3 ml of dichloromethane is added methyl fluorosulfonate (0.160 ml, 1.97 mmole) at room temperature. The reaction is followed by UV assay of removed aliquots of the solution. After two hours, a yellow oil separates and the UV absorbance at 318 nm of the dichloromethane layer drops to 4% of original. The upper layer is decanted and the lower layer washed two times with 5 ml

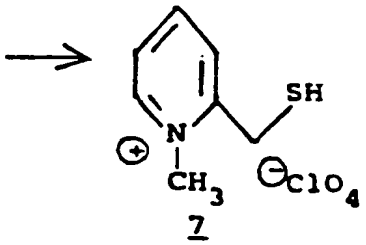
portions of dichloromethane. The residual oil is assayed by UV for 3 then pumped to a foam in vacuo. The crude 3 thus produced is dissolved in a mixture of 6 ml of N,N-dimethylacetamide, 37 ml n-butanol, 19 ml ethyl acetate and 37 ml 0.5N N-methylmorpholine-HCl pH 7.0 buffer and 280 mg of 20% palladium hydroxide on carbon added. The mixture is hydrogenated at 42 psi with shaking for 70 minutes. At the end of this period, the mixture is removed, filtered through a prewashed celite bed with 5 to 10 ml water and the organic phase discarded. The aqueous phase is washed with 2 X 50 ml of dichloromethane and concentrated in vacuo to a volume of 23 ml. The solution of crude product is charged onto a 2.8 X 38 cm column of Dowex 50-X4 (Na^+ cycle) at 5° and eluted with water. The eluate is monitored by UV and fractions containing the desired product are pooled, concentrated to 150 ml and lyophilized to yield 272 mg of final product 4.

Step C.

Preparation of 1-methyl-2-mercaptomethyl-pyridinium perchlorate 7.



5 6



7

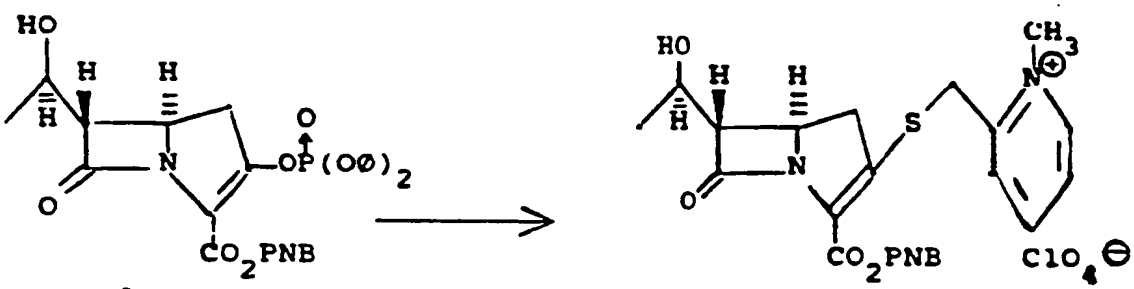
To a solution of 2-picolyl chloride hydrochloride (5.00 g, 30.5 mmol) and potassium thio acetate (4.18 g, 36.6 mmol) in 50 ml N,N-dimethyl-formamide, triethylamine (4.25 ml, 30.5 mmol) is added slowly to yield a pink solution. The mixture is heated to 80° and held there for 2 hours, after which time the solvent is removed in vacuo to yield a brown oil. The residue is taken up in ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered and concentrated to yield crude 5 as a dark oil (5.0 g).

Thioester 5 (2.0 g, 12 mmol) is dissolved in 10 ml N,N-dimethylformamide under nitrogen and methyl iodide (7.5 ml, 120 mmol) is added dropwise. The mixture is stirred 20 hours at room temperature, then the solvent is removed in vacuo to yield a brown powder which is triturated with dichloromethane, filtered and dried in vacuo to yield 2.21 g of 6 as a tan powder. Additional material (1.07 g) is obtained by concentration of an aqueous extract of the dichloromethane wash from the trituration step. (nmr (D_2O) δ 2.49 (s); 4.42 (s); 7.9 to 9.0 (m).

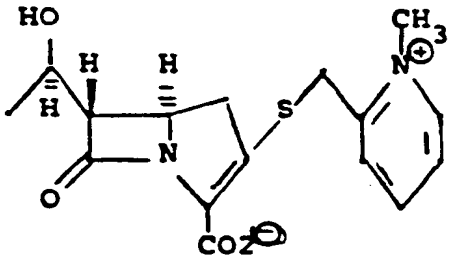
Pyridinium thioester 6 (102.7 mg, 0.33 mmol) is suspended in 0.63 ml 2N methanolic perchloric acid and stirred at room temperature under nitrogen for 66 hours. The resulting tan suspension is filtered and the solid washed with ether to give 51.7 mg of thiol 7 as a tan powder (nmr (D_2O) δ 4.23 (s); 4.43 (s), 7.8 to 8.6 (m).

Step D

Preparation of (5R,6S)-6-(1(R)-hydroxyethyl)-2-(1-methyl-2-pyridinium)methylthio-carbapen-2-em-3-carboxylate 4.



1 3



4

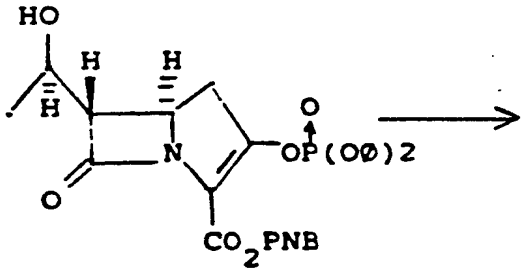
To a solution of vinyl phosphate 1 (58 mg, 0.1 mmol) and thiol 7 (34.9 mg) in 0.32 ml of N,N-dimethylacetamide at -20° under nitrogen is added N,N-diisopropylethylamine (34.8 µl, 0.2 mmol). The mixture is aged 25 minutes at -20° then transferred directly to a hydrogenation vessel with 1.9 ml i-propanol, 1.0 ml ethyl acetate and 1.9 ml water. Phosphate buffer (pH 7, 0.1M, 1.0 ml) and 20% palladium hydroxide on carbon (15 mg) is added and the mixture hydrogenated at 46 psi for two hours. The catalyst is removed by filtration and the filtrate diluted with 5 ml ethyl acetate and 5 ml

water. The aqueous phase is separated, washed with ethyl acetate, concentrated to ca. 1 ml *in vacuo* and the product purified by chromatography on Dowex 50 -X4 (Na^+) as described above to yield 6.3 mg of product 4.

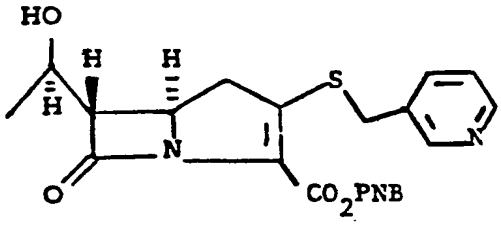
EXAMPLE 2

Step A.

Preparation of p-Nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-(3-pyridylmethylthio)-carbapen-2-em-3-carboxylate 8.



1



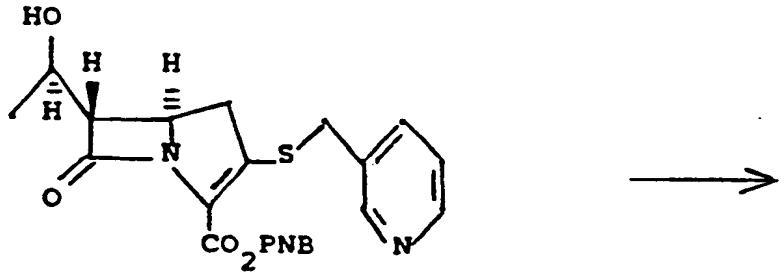
8

To a solution of p-nitrobenzyl (5R,6S)-6-(1R-hydroxyethyl)-2-diphenylphosphonoxy-carbapen-2-em-3-carboxylate 1 (116 mg) in acetonitrile (0.3 ml)

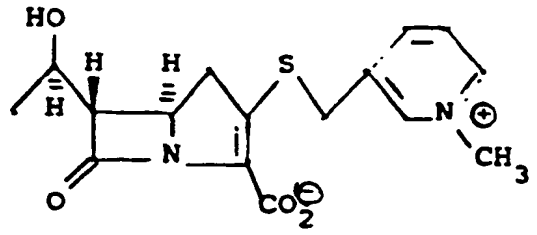
cooled in an ice-bath, is added diisopropylethylamine (35 ml) and 3-mercaptomethylpyridine (25 µl). A precipitate forms within a few minutes. After one hour the mixture is diluted with methylene chloride and filtered. The filter cake is washed with methylene chloride and dried by suction leaving substantially pure p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-(3-pyridylmethylthio) carbapen-2-em-3-carboxylate (52 mg). The combined filtrates are washed twice with pH7 phosphate buffer, dried over anhydrous magnesium sulfate and evaporated to give an additional 17 mg of crystalline product 8. Total yield 77%. TLC, silica gel, 5% MeOH/$CHCl_3$. R_f = 0.21.

Step B.

Preparation of (5R,6S)-6-(1-R-hydroxyethyl)-2-(1-methyl-3-pyridiniummethylthio)-carbapen-2-em-3-carboxylate 9.



8



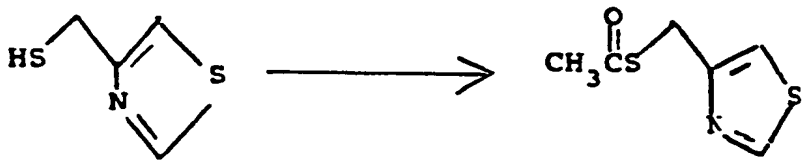
9

To a suspension of p-nitrobenzyl (5R,6S)-6-(1-(R)-hydroxyethyl)-2-(3-pyridylmethylthio)-carbapen-2-em-3-carboxylate (61 mg) in methylene chloride (2 ml) is added methyl fluorosulfonate (12 µl). The mixture is stirred at room temperature for one hour. The solid changes appearance without dissolving. The solvent is evaporated in a stream of nitrogen leaving a powder consisting of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-(1-methyl-3-pyridiniummethylthio)-carbapen-2-em-3-carboxylate fluorosulfonate salt. This is dissolved in a mixture of 8 ml THF and 8 ml of 0.05M pH 7 phosphate buffer and hydrogenated in the presence of 40 mg of 10% Pd/C catalyst at 45 psi for 2 hours. The catalyst is filtered and the filtrate is extracted once with 30 ml of ether. The aqueous solution is adjusted to pH 6.8 by the addition of solid sodium bicarbonate and applied to an ice-water jacketed column (1.5 X 24 cm)of Dowex 50, Na^+ cycle resin (200 to 400 mesh). The column is eluted with de-ionized water taking 20 ml fractions. Fractions 6 to 10 are combined, concentrated to 10 ml and lyophilized giving the titled product 9 as a cream colored powder (50 mg). U.V. λmax at 265 and 296 nm of equal intensity E% 233, 86% NH_2OH extract. NMR (D_2O)δ 1.26 (d, J=6.5 Hz), 3.02 (dd, J=9 and 18 Hz), 3.15 (dd, J=10 and 18 Hz), 3.39 (dd, J=2.8 and 6Hz), 4.2 (m), 4.3 (ABq), 4.4 (s), 8.04, 8.57, 8.9 (ar).

EXAMPLE 3

Step A.

Preparation of 4-(acetylthiomethyl)thiazole 10.

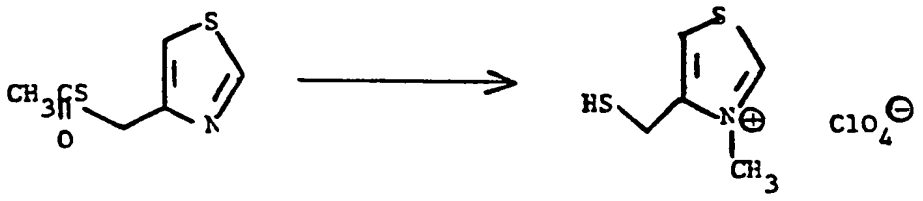


10

To an ice-cooled solution of 4-thiomethylthiazole (2g, 0.0152 mole) in methylene chloride (20 ml) is added triethylamine (2.1 ml, 0.0152 mole) and acetyl chloride (1.08 ml, 0.0152 mole). A precipitate forms immediately and after 10 minutes the mixture is filtered, washed twice with pH 7 phosphate buffer, dried over anhydrous magnesium sulfate and evaporated. Distillation of the residue at 7mm/117-119°C gave 2.23 g of the title compound as a clear liquid. 86% yield.

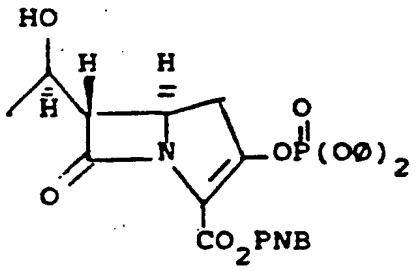
Step B.

Preparation of 3-methyl-4-thiomethylthiazolium perchlorate 11.

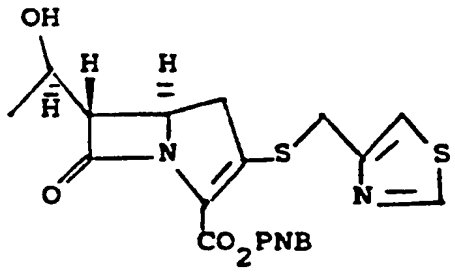


10 11

To an ice-cooled solution of 4-acetylthiomethylthiazole (1g, 0.0058 mole) in acetonitrile (5 ml) is added methylfluorosulfonate (0.49 ml, 0.0058 mole) dropwise. The reaction is warmed to room temperature and gives 1.5 g of a white solid upon treatment with ether. The solid is suspended in methanolic 2N $HClO_4$ and slowly dissolves over 18 hours at room temperature. The title compound (0.23g, 84% yield) is collected upon addition of ether.



1



12

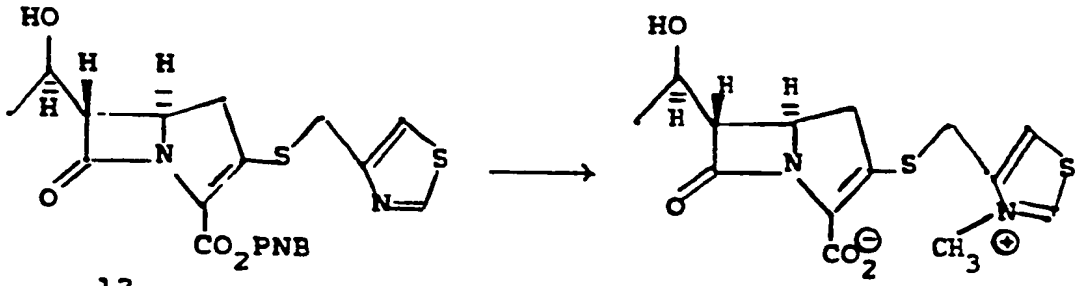
Step C.

Preparation of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-(4-thiazolylmethylthio)-carbapen-2-em-3-carboxylate 12

p-Nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-diphenylphosphonoxy-carbapen-2-em-3-carboxylate 1 (0.406 g, 0.70 mmoles) is dissolved in anhydrous acetonitrile (3 cc) and is cooled in an ice-bath under N_2. Diisopropylethylamine (122 µl, 0.70 mmoles) and 4-thiomethylthiazole (70 µl, 0.70 mmoles) are added simultaneously and a precipitate forms within a few minutes. After 30 minutes the mixture is filtered and the collected solid is washed with ethyl acetate giving 0.21 g of the title compound 12, yield 69%.

Step D.

Preparation of (5R,6S)-6-(1-R-hydroxyethyl)-2-(3-methyl-4-thiazoliummethylthio)carbapen-2-em-3-carboxylate 13.



12 13

To an ice-cooled suspension of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-(4-thiazolylmethylthio)-carbapen-2-em-3-carboxylate 12 (.45 g, 0.1 mmoles) in acetonitrile (1cc) is added methyl

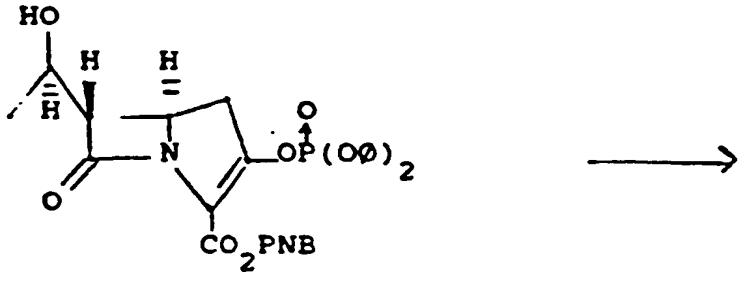
fluorosulfonate (8.5 µl, 0.1 mmoles). The mixture is warmed to room temperature and the solid gradually dissolved over 30 minutes. The solvent is then evaporated in a stream of nitrogen and the resulting semi-solid is dissolved in tetrahydrofuran (8 ml), pH 6.5 phosphate buffer (4 ml) and H_2O (4 ml) and is hydrogenated for 2 hours at 45 psig in the presence of 10% Pd/C (50 mg). The catalyst is filtered and the filtrate is washed once with ether. The aqueous layer (pH 6.2) is concentrated to 5cc and is placed on a column (27.5 x 1.5 cm) of Dowex 50W-X4 200-400 mesh sodium-cycle resin. The column is eluted with de-ionized water and the fractions between 100 ml and 270 ml are collected, concentrated to 8 cc and lyophillized to give 10 mg of 13 as a light yellow powder.

UV (H_2O) λ max at 245 and 295.

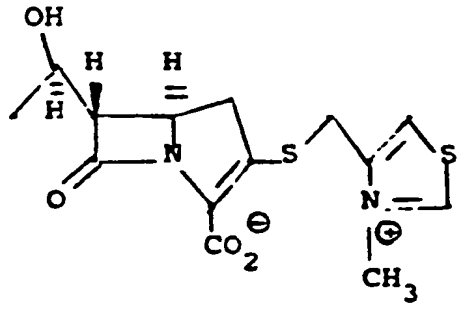
NMR (selected resonances) (D_2O) δ 1.28 (3H, d, J=6.5Hz), 3.42 (1H, dd, J=2.8, 6.1 Hz), 4.25 (3H, s).

Step E.

(5R,6S)-6-(1-R-hydroxyethyl)-2-(3-methyl-4-thiazolium methylthio)-carbapen-2-em-3-carboxylate 13.



1



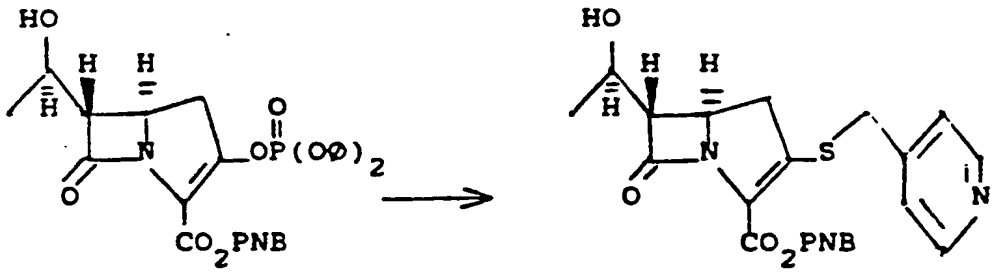
13

A solution of p-nitrobenzyl (5R,6S)-6-(1-R-hydroxyethyl)-2-diphenylphosphonoxy-carbapen-2-em-3-carboxylate 1 (7.43 g, 0.0128 mole) in N,N-dimethylacetamide (38 ml) is cooled to -20°C in an ethylene glycol/H_2O/dry ice mixture and is treated with 3-methyl-4-thiomethylthiazolium perchlorate 11 (3.13 g, 0.0128 mole) and diisopropylethylamine (2.2 g, 0.0128 mole). After 30 minutes the reaction mixture is added to butanol (200 cc), ethyl acetate (120 cc), de-ionized water (200 cc) and pH 6.8 0.5N N-methylmorpholine buffer (350 cc) and is hydrogenated for 2 hours in the presence of 5 g of

20% $Pd(OH)_2/C$. The catalyst is filtered and the filtrate is washed several times with methylene chloride. The pH is adjusted to 6.7 with solid sodium bicarbonate and the aqueous layer is placed on a (9.75 X 23 cm) Dowex 50W-X4 200-400 mesh sodium cycle column. The column is eluted with de-ionized water and a center-cut fraction is taken, concentrated and lyophilized to give 3.1g of the title compound 13 as a light yellow powder.

EXAMPLE 4

Step A: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-pyridylmethylthio)-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate (14)



1 14

A suspension of p-nitrobenzyl (5R,6S)-2-(diphenylphosphono)oxy-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate (2.50 g, 4.31 mmol) and 4-pyridine-methanethiol hydrochloride (0.73 g, 4.52 mmol) in anhydrous acetonitrile (9.0 ml) was cooled in an ice-water bath and treated with N,N-diisopropyl-ethylamine (1.6 ml, 9.05 mmol). A solution formed which rapidly developed into a suspension. After stirring at 0° for 30 minutes, the suspension was filtered and the white solid washed with cold

acetonitrile and vacuum dried to provide the title compound 14 (1.71 g).

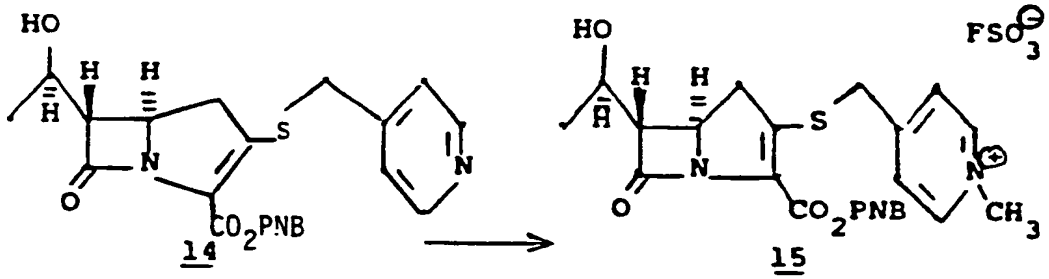
NMR (DMSO d_6) δ1.13 (d, J=6.3Hz, $C\underline{H}_3CH$), 3.1-3.4 (m, $CHC\underline{H}_2$, H6), 3.95 (sextet, J 6Hz, $C\underline{H}OH$), 4.13 (dt, J=9.4, 2.7Hz, H5), 4.25 (ABq, J=14.2Hz, SCH_2), 5.09 (d, J=4.9Hz, $CHO\underline{H}$), 5.38 (ABq, J=14.2Hz, CH_2Ar), 7.41 (dd, J=4.5, 1.5Hz, pyr), 7.70 (d, J=8.8Hz, Ar), 8.24 (d, J=8.8Hz, Ar), 8.55 (dd, J=4.5, 1.5Hz, pyr).

IR (Nujol) 3150, 1785, 1680, 1595 cm^{-1}

UV (p-dioxane) λ max 319 nm (ϵ12,700), 265 nm (ϵ12,800)

m.p. 159-160°(dec)

Step B: Preparation of p-Nitrobenzyl (5R,6S)-2-(1-methyl-4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate fluorosulfonate (15)



14 → 15

A suspension of p-nitrobenzyl (5R,6S)-2-(4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate 14 (1.70 g, 3.73 mmol) in dichloromethane (37 ml) was cooled in an ice-water bath and treated with methyl fluorosulfonate (0.32 ml, 3.93 mmol). After stirring at 0° for 1 hour, the reaction had deposited a viscous yellow oil. The

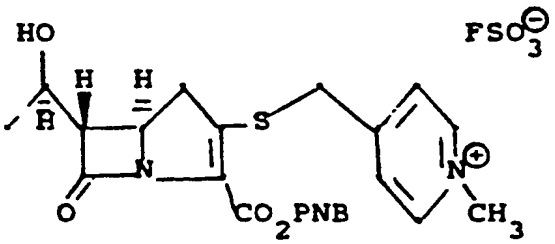
dichloromethane was decanted and the residue washed with dichloromethane and briefly pumped under vacuum. The residue was triturated with i-propanol to give a yellow solid which was recovered by filtration and vacuum dried to afford the title compound 15 (2.08 g).

NMR (DMSO-d_6) δ 1.12 (d, J=6.2Hz, $C\underline{H}_3CH$), 3.12 (dd, J=18.6, 8Hz, $CHC\underline{H}_A H_B$), 3.3 (dd, J=18.6, 10.0Hz, $CHCH_A\underline{H}_B$), 3.30 (dd, J=6.3, 3Hz, H6), 3.95 (p, J 6Hz, $C\underline{H}OH$), 4.11 (dt, J=9.3Hz, H5), 4.31 (s, NCH_3), 4.50 (s, CH_2, Pyr), 5.38 (ABq, J=14.2Hz, CH_2Ar), 7.71 (d, J=8.7Hz, $ArNO_2$), 8.13 (d, J=6.6Hz, Pyr), 8.25 (d, J=8.7Hz, $ArNO_2$), 8.91 (d, J=6.6Hz, Pyr).

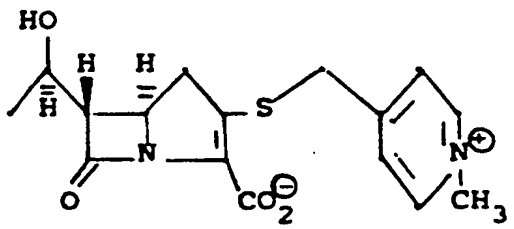
IR (Nujol) 3520, 1765, 1690, 1645, 1600 cm^{-1}

UV (MeOH) λ max 314 (ϵ11,000), 262 (ϵ13,200)

Step C: Preparation of p-Nitrobenzyl (5R,6S)-2-(1-methyl-4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (16)



15



16

A solution of p-nitrobenzyl (5R,6S)-2-(1-methyl-4-pyridiniummethylthio)-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate 15 (1.90 g, 3.34 mmol) in N-ethylpyrrolidinone (19 ml) was mixed with n-butanol (66 ml), ethyl acetate (32 ml), water (66 ml), and 0.5M pH 7.0 N-methylmorpholine-hydrochloric acid buffer. The resulting two phase mixture was treated with 20% palladium hydroxide on carbon (1.9 g) and hydrogenated on a Parr shaker at 45 psi for 75 minutes. The mixture was filtered through a celite pad and the organic phase which separated was discarded. The aqueous phase was washed twice with dichloromethane and concentrated under vacuum to ca. 48 ml. This solution was charged onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 5.0 cm diameter x 30 cm) which was eluted with water in a cold room at 20 ml fractions/1.0 minute. Fractions 105-180 which contained product were combined, concentrated under vacuum and lyophilized to afford the title compound 16 (189 mg) as a light tan-colored fluff.

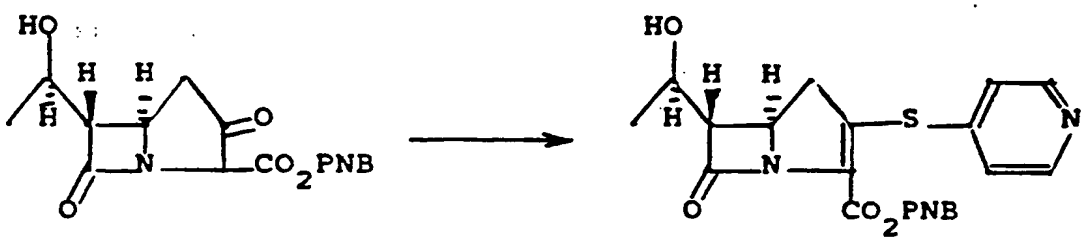
NMR (D_2O) δ 1.25 (d, J=6.3Hz, $C\underline{H}_3CH$), 3.02 (dd, J=17.3, 8.7Hz, $CHC\underline{H}_A\underline{H}_B$), 3.07 (dd, J=17.3, 9.5Hz, $CHCH_A\underline{H}_B$), 3.37 (dd, J=5.9, 2.7Hz, H6), 4.11 (dt, J=9.2, 2.4Hz, H5), 4.20 (p, J 6Hz, $C\underline{H}OH$), 4.36 (s, NCH_3), 8.06 (d, J=6.7Hz, pyr), 8.71 (d, J=6.7Hz, pyr).

IR (Nujol) 3350 (br), 1758, 1641, 1587 cm^{-1}

UV (water) λmax 297 nm (ϵ7,710), 258 (ϵ6,850); (water + $NH_2OH.HCl$) extinguished λmax 296 nm (6,850)

EXAMPLE 5

Step A: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-pyridylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (17)



17

A solution of p-nitrobenzyl (5R,6S)-6[1(R)-hydroxyethyl]-2-oxocarbapenam-3(R)-carboxylate (200 mg, 0.574 mmol) in acetonitrile (0.60 ml) was treated at ice-water bath temperature with diphenylchlorophosphate (0.125 ml, 0.603 mmol) and N,N-diisopropylethylamine (0.119 ml, 0.683 mmol). After stirring at 0° for 25 minutes, the reaction was treated with additional N,N-diisopropylethylamine (0.110 ml, 0.612 mmol) and a solution of 4-mercaptopyridine (95.6 mg, 0.816 mmol) in N,N-dimethylformamide (0.7 ml) and acetonitrile (2.2 ml). The reaction solution was stirred 3.5 hours at 0° and diluted with ethyl acetate. The solution was washed with 5% aqueous sodium bicarbonate solution, dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum to provide the title compound as a foam (286 mg).

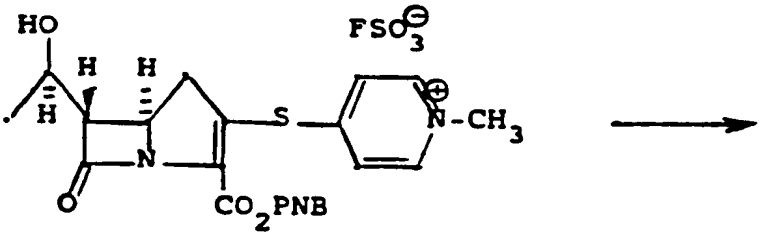
The crude product was chromatographed on a column of silica gel (29 g) eluted with 10% ethanol in ethyl acetate. Fractions containing compound 17 were combined and concentrated to a foam (147 mg) under vacuum.

NMR (DMSO-d_6) δ 1.09 (d, J=6.5Hz, $C\underline{H}_3CH$), 2.82 (dd, J=10.1, 18.0Hz, $CHCH_{\underline{A}}B_B$), 3.05 (dd, J=8.3, 18.0Hz, $CHCH_A\underline{CH}_B$), 3.38 (dd, J=3.0, 5.8Hz, H6), 3.96 (sextet, J 6Hz, $C\underline{H}OH$), 4.15 (dt, J=3.0, 8Hz, H5), 5.06 (d, J=5.0, Hz, $CHO\underline{H}$), 5.46 (ABq, J=14.0Hz, CH_2Ar), 7.65 (dd, J=1.4, 4.5Hz, pyr), 7.77 (d, J=8.9Hz, $ArNO_2$), 8.30 (d, J=8.9Hz, $ArNO_2$), 8.65 (dd, J=1.4, 4.5Hz, pyr).

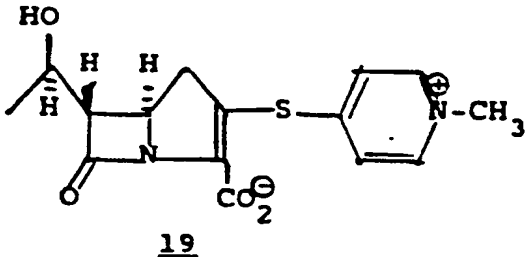
IR (CH_2Cl_2) 1770, 1718, 1690 cm^{-1}

ms 441 (M^+), 330 (M^+ - C_5H_5NS), 246 (330 - $C_4H_4O_2$), 111 (246 - $C_7H_5NO_2$).

Step B: Preparation of p-Nitrobenzyl (5R,6S)-2-(4-pyridylthio)-6[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (19)



18



19

A solution of p-nitrobenzyl (5R,6S)-2-(4-pyridylthio)-6[1(R)-hydroxyethyl]-carbapen-2-em-3-carboxylate 17 (70 mg, 0.17 mmol) in dichloromethane

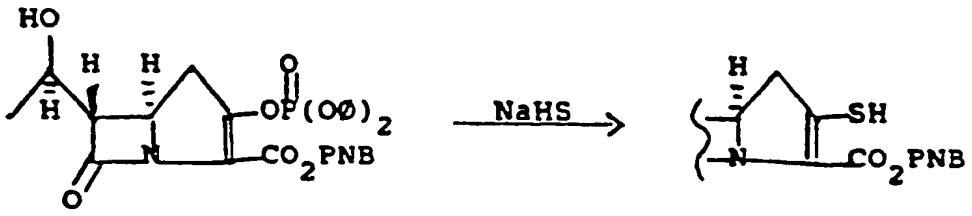
(3.0 ml) was stirred in an ice-water bath and treated with methyl fluorosulfonate (21 µl, 0.26 mmol). After stirring 15 minutes, the cold solution was mixed with ether (10 ml) and filtered. The recovered quaternary salt 18 was dissolved in tetrahydrofuran (3.5 ml) and aqueous 0.1N pH 2.1 phosphate buffer (3.5 ml). The solution was treated with 10% palladium on carbon and hydrogenated on a Parr shaker at 45 psi for 1 hour. The catalyst was removed by centrifugation and the decanate was diluted with water (2 ml), and washed with ethyl acetate. The aqueous phase was briefly concentrated under vacuum to ca. 5 ml and charged onto a column of Dowex 50W-X4 (sodium form, 200-400 mesh, 1.5 x 36 cm). The column was eluted with water in a cold room at 6.0 ml fractions/2.5 minutes. Fractions 27 to 47 which contained product were combined, concentrated under vacuum, and lyophilized to afford the title compound 19 (7 mg).

NMR (D_2O) δ 1.30 (d, J=6.5Hz, $CHC\underline{H}_3$), 3.08 (dd, J=8.9, 17.8Hz, $CHCH_A\underline{H}_B$), 3.22 (dd, J=10.0, 17.8Hz, $CHCH_A\underline{H}_B$), 3.64 (dd, J=3.1, 6Hz, H6), 4.25 (s, $N-CH_3$), 4.30 (p, J 6Hz, $C\underline{H}OH$), 4.43 (dt, J=3.1, 9.5Hz, H5), 7.83 (d, J=7.5Hz, pyr), 8.50 (d, J=7.5Hz, pyr).

UV (water) λmax 303 nm (ϵ9,820).

EXAMPLE 6

Step A: Preparation of p-Nitrobenzyl (5R,6S)-6[1(R)-hydroxyethyl]2-[(1-methyl-5-imidazolyl)methyl-thio]carbapen-2-em-3-carboxylate (20)



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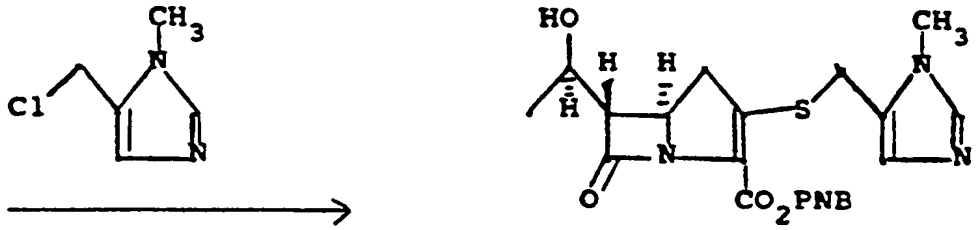


20

A solution of vinyl phosphate 1 (674 mg, 1.16 mmol) in anhydrous N,N-dimethylformamide (DMF, 3.9 ml) was cooled in a dry ice-acetonitrile bath (-40°C) under a N_2 atmosphere and treated dropwise over 2 minutes with a solution of sodium hydrogen sulfide (68.4 mg, 1.22 mmol) in DMF (2 ml). The reaction mixture was treated with N,N-diisopropyl-ethylamine (0.647 ml, 3.72 mmol), stirred at -40°C for 20 minutes, then treated dropwise with a solution of 1-methyl-4-chloromethylimidazole hydrochloride (203.6 mg, 1.22 mmol) in DMF (2.4 ml). After stirring an additional 20 minutes at -40°C, the reaction mixture was diluted with ethyl acetate (100 ml), washed with water (4 x 100 ml) and brine, dried

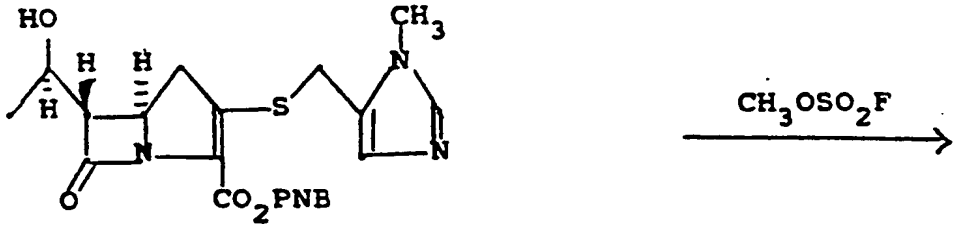
with $MgSO_4$, filtered, and evaporated in vacuo to give a yellow-brown solid (367 mg). This material was triturated with 1:1 ethyl acetate-ether and dried in vacuo to afford the title compound 20 (250 mg, 47%) as a yellow-brown solid.

IR (Nujol) ν max 1769, 1690, 1517, 1333 cm^{-1};

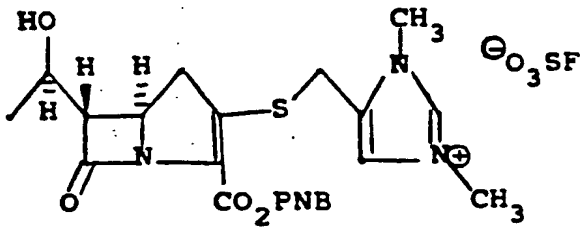
UV (dioxane) λ max 319 nm (ϵ12,600), 267 (11,900);

NMR ($CDCl_3$) δ 1.37 (d, J=6.3Hz, CH_3CHOH), 3.14 (dd, J=17.8 and 8.6Hz, $CHCHaHb$), 3.21 (dd, J=2.7 and 6.7Hz, H6), 3.42 (dd, J=17.8 and 9.7Hz, $CHCHaHb$), 3.68 (s, NCH_3), 4.03, 4.12 (ABq, J=14.6Hz, SCH_2), 4.25 (m, H5 and CH_3CHOH), 5.23, 5.50 (ABq, J=13.8Hz, CH_2Ar), 7.00 (s, imidazole-H), 7.47 (s, imidazole-H), 7.65 (d, J=8.7Hz, 2 ArH), 8.22 (d, J=8.7Hz, 2ArH).

Step B: Preparation of p-Nitrobenzyl (5R,6S)-6[1(R)-hydroxyethyl]2-[(1,3-dimethyl-4-imidazolium)-methylthio]carbapen-2-em-3-carboxylate fluoro-sulfate (21)



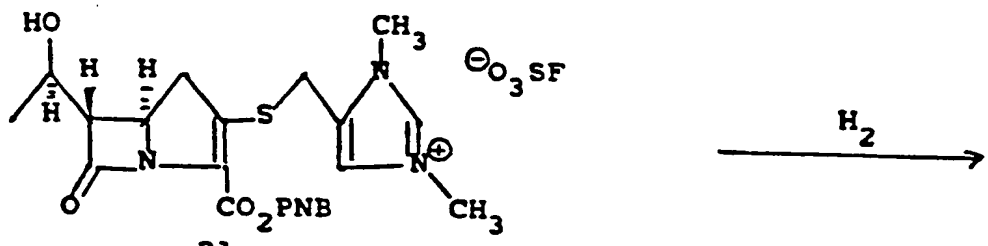
20



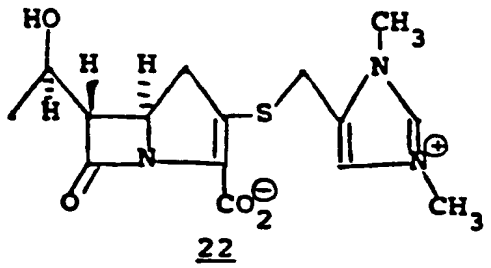
21

A solution of carbapenem derivative 20 (223.6 mg, 0.49 mmol) in anhydrous methylene chloride (10 ml) was cooled in an ice-bath and stirred under a nitrogen atmosphere while a solution of methyl fluorosulfate (0.042 ml, 0.52 mmol) in methylene chloride (2 ml) was added dropwise over 5 minutes. A gummy precipitate formed which, on continued stirring at 0°C, gave way to a fine, cream colored solid. After 30 minutes, the solid was collected, washed with methylene chloride (2 x 10 ml), and dried in vacuo to give 21 (228 mg) as a cream colored powder. IR (Nujol) ν max 1767, 1691, 1620, 1290 cm^{-1}; UV (10:1 dioxane-water) λmax 316 nm (ϵ12,500), 271 (11,300).

Step C: Preparation of (5R,6S)-6[1(R)-hydroxyethyl]-2-[(1,3-dimethyl-4-imidazolium)methylthio]-carbapen-2-em-3-carboxylate (22)



21



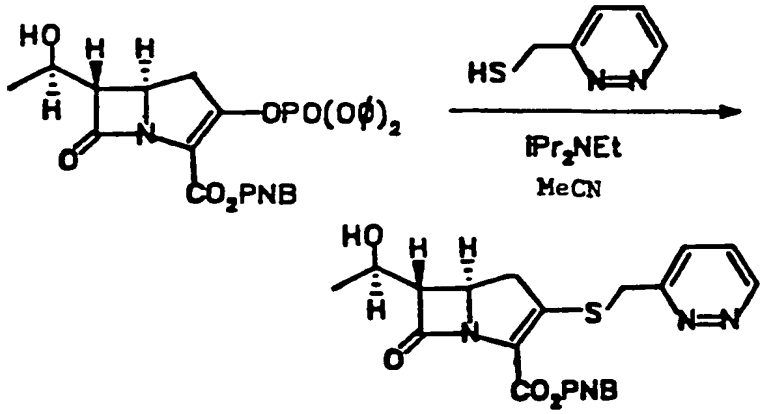
22

The imidazolium salt 21 (221 mg, 0.386 mmol) was taken up in a mixture of n-butanol (20 ml), ethyl acetate (10 ml), water (20 ml), and 0.5M pH 6.8 N-methylmorpholine-hydrochloric acid buffer (10 ml), treated with 20% palladium hydroxide on carbon (100 mg), and hydrogenated at 45 psi for one hour. The mixture was filtered through a celite pad to remove the catalyst which was washed with additional water. The aqueous portion of the filtrate was washed three times with methylene chloride, concentrated in vacuo to ca. 3 ml, and loaded onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 2.5 x 34 cm) which was eluted with de-ionized water in a cold room at 400 drop fractions every 5.1 minutes. The product containing fractions (23-32, 242 ml) were located by uv, concentrated in vacuo, and lyophilized to yield the title compound 22 (69 mg) as a white, amorphous solid.

IR (Nujol) ν max 3400 (br), 1750, 1590 cm^{-1};
uv (0.05M pH 7.0 MOPS) λmax 297 nm (96% NH_2OH extinguished, ϵ ext. 7,900);
NMR (D_2O) δ 1.28 (d, J=6.4Hz, $C\underline{H}_3CHOH$), 3.09 (dd, J=8.6 and 17.5Hz, $CHC\underline{H}aHb$), 3.24 (dd, J=9.5 and 17.4Hz, $CHCHaC\underline{H}b$), 3.42 (dd, J=2.6 and 6.0Hz, H6), 3.85 (s, NCH_3), 3.86 (s, NCH_3), 4.07, 4.21 (ABq, J=15.5Hz, SCH_2), 4.18 (m, H5), 4.23 (pentet, J=6.4Hz, $CH_3C\underline{H}OH$), 7.43 (brs, imidazole-H), 8.66 (brs, imidazole-H).

EXAMPLE 7

Step A:



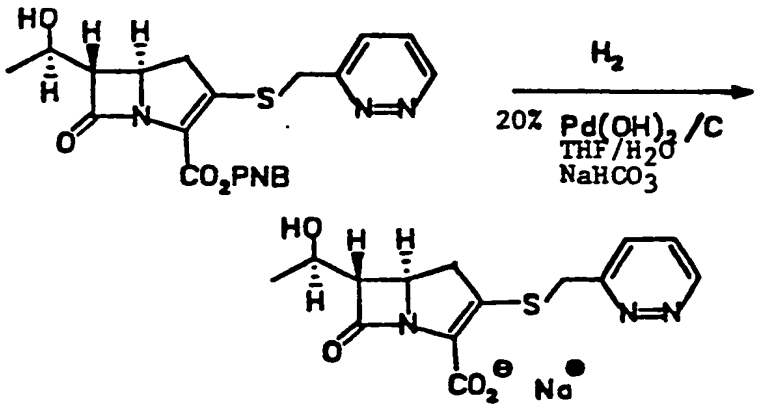
p-Nitrobenzyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em 3-carboxylate

A solution of p-nitrobenzyl (5R,6S)-2-(diphenylphosphono)oxy-6-[1(R)-hydroxyethyl]carbapen-2-em 3-carboxylate (540 mg, 0.93 mmol) in anhydrous acetonitrile (5 cc) was cooled in an ice-bath under a nitrogen atmosphere and was treated with N,N-diisopropylethylamine (162 µl, 0.93 mmol) followed by the dropwise addition of 3-mercaptomethylpyridazine*(117 mg, 0.93 mmol). A solid rapidly precipitated and after 30 minutes the suspension was diluted with ethyl acetate and was filtered giving the title compound (308 mg) as a white solid. The mother

* 3-Mercaptomethylpyridazine
K. Yu. Novitsuii, N. K. Sadovaya, E. F. Kas'Yanova, L. K. Semna, Khimiya Geterotsiklicheskikh Soedinenii Vol 6, No. 3, pp 412-414 (1970).

liquors were washed with 0.1N pH 7 phosphate buffer, dried over magnesium sulfate, filtered and evaporated under vacuum. The residue was chromatographed on a 1 mm x 20 cm x 20 cm silica gel GF plate, using 5% ethanol-methylene chloride as a developing solvent, to give additional product (28 mg) as a white solid.
mp 156°C (dec) Thomas Hoover Capillary Melting Point Apparatus (uncorrected)
IR (Nujol) ß-lactam ν max 1740 cm^{-1}
NMR ($CDCl_3$) δ 1.31 (d, J=6.1 Hz, $\underline{CH_3}CHOH$), 3.09 (dd, J=8.9, 18.1 Hz, $C\underline{H_a}H_b$), 3.17 (dd, J=2.8, 6.5 Hz, H6), 3.61 (dd, J=9.8, 18.1 Hz, $CH_a\underline{H_b}$), 4.20 (m, H5), 4.20 (m, $CH_3\underline{CH}OH$), 4.28+4.31 (ABq, J=14.8 Hz, $S-CH_2$), 5.21+5.48 (ABq, J=14.0 Hz, CH_2Ar), 7.52 (dd, J=5.0, 8.0 Hz, pyridazinyl H5), 7.63 (d, J=8.8 Hz, 2ArH), 7.64 (d, J=8.4 Hz, pyridazinyl H4), 8.22 (d, J=8.8 Hz, 2ArH), 9.13 (d, J=5.0 Hz, pyridazinyl H6).

STEP B:



Sodium (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio]carbapen-2-em carboxylate

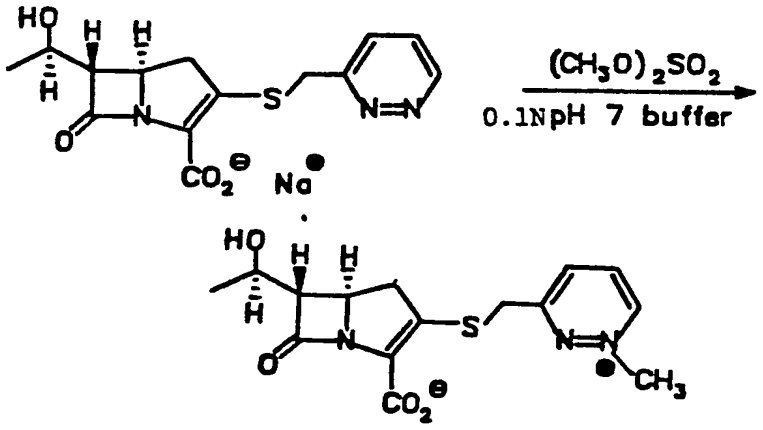
A suspension of p-nitrobenzyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em 3-carboxylate (5.5 g, 0.012 mol) in a mixture of water (0.75 L), containing sodium bicarbonate (1.01 g, 0.012 mol), and tetrahydrofuran (0.75 L), was hydrogenated for 2 hours at 40 psig in the presence of 20% $Pd(OH)_2/C$ (1 g). The mixture was filtered through Solka-Floc and the solution was washed with ethyl ether. The aqueous phase concentrated under vacuum to ca. 500 cc and was freeze-dried giving (3.80 g) of a yellow solid. Crystallization from methanol gave the title compound (3.57 g) as an off-white solid.

IR (Nujol) ß-lactam ν max 1740 cm^{-1}

UV (H_2O) λ max 299 (ϵ 8,870) 93% H_2NOH extinguished

NMR (D_2O) δ 1.26 (d, J=6.5 Hz, $C\underline{H}_3CHOH$), 2.99 (dd, J=8.8, 17.8 Hz, $CH_a\underline{H}_b$), 3.23 (dd, J=9.8, 17.6 Hz, $CH_a\underline{H}_b$), 3.36 (dd, J=2.8, 5.9 Hz, H6), 4.14 (m, $CH_3\underline{CH}OH$), 4.14 (m, H5), 4.28+4.42 (ABq, J=14.8 Hz, S-CH_2), 7.83 (dd, J=4.8, 8.4 Hz, pyridazinyl H5), 7.99 (d, J=8.6 Hz, pyridazinyl H4), 9.12 (d, J=4.8 Hz, pyridazinyl H6).

STEP C:



5R,6S-(1(R)-Hydroxyethyl)-2-(1-methyl-3-pyridazinium-methylthio)carbapen-2-em 3-carboxylate

A solution of sodium (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridazinylmethylthio)carbapen-2-em 3-carboxylate (1.0 g, 0.0029 mol) in 0.1N pH 7 phosphate buffer (20 cc) was cooled in an ice-bath and treated with dimethylsulfate (2.2 ml, 0.023 mol). The mixture was stirred rapidly in the cold for 120 minutes, while incremental amounts of 1N NaOH were added in order to maintain a pH range of 6.8 to 7.2. The suspension was washed with ethylether and was loaded on a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 2.5 cm x 37 cm). The ice-cooled jacketed column was eluted with de-ionized water and 25 cc fractions were collected. Fractions 23-63 were combined, concentrated under vacuum to 80 cc and lyophilized to give 0.55 g of a yellow solid. This material was crystallized from ethanol-water to give the title compound (0.47 g) as fine yellow needles.

IR (Nujol) ß-lactam ν max 1750 cm^{-1}

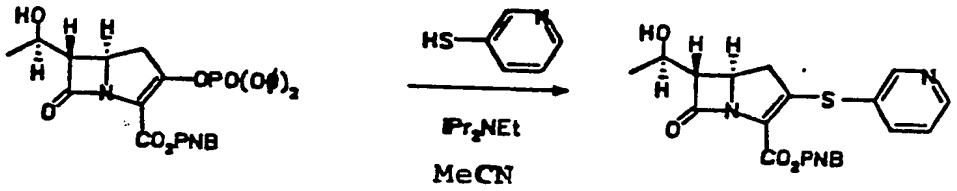
UV (H_2O) λ max 293 (ϵ8,610) 89% H_2NOH extinguished

NMR (D_2O) δ 1.27 (d, J=6.5 Hz, $\underline{CH_3}CHOH$), 3.10 (dd, J=8.5, 17.5 Hz, $C\underline{H_a}H_b$), 3.30 (dd, J=9.8, 17.7 Hz, $CH_a\underline{H_b}$), 3.43 (dd, J=2.8, 5.9 Hz, H6), 4.21 (m, $CH_3\underline{CH}OH$), 4.21 (m, H5), 4.38+4.50 (ABq, J=15.7 Hz, $S-CH_2$), 4.64 (s, $N-CH_3$), 8.51 (dd, J=5.4, 8.2 Hz, pyridazinyl H5), 8.60 (d, J=8.0 Hz, pyridazinyl H4), 9.58 (d, J=5.5 Hz, pyridazinyl H6).

Anal. Calc'd for $C_{15}H_{17}N_3O_4S.2\text{-}1/2H_2O$:
C, 47.36; H, 5.83; N, 11.04
Found: C, 47.32; H, 5.77; N, 10.77.

EXAMPLE 8

STEP A:



p-Nitrobenzyl (5R,6S)-6-[(1(R)-hydroxyethyl]-2-(3-pyridylthio)-carbapen-2-em-3-carboxylate

A solution of p-nitrobenzyl (5R,6S)-2-(diphenylphosphono)oxy 6-[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (434 mg, 0.75 mmol) in anhydrous acetonitrile (2 ml) was cooled to ca. -20°C under a nitrogen atmosphere and treated dropwise over 5 minutes with a solution of 3-mercaptopyridine (108 mg, 0.97 mmol) in acetonitrile (1 ml) followed by N,N-diisopropylethylamine (0.169 ml, 0.97 mmol). After stirring in the cold for 30 minutes, the mixture was diluted with ethyl acetate, washed with water and brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to give a pale yellow foam (343 mg). This material was dissolved in a small volume of ethyl acetate and the solution was diluted with ethyl ether and scratched to give the title compound (84 mg) as an off-white solid. The mother liquors were concentrated and chromatographed on three 1 mm x 20 x 20 cm silica gel GF plates using ethyl acetate as developing solvent to give additional product (113 mg) as a foam. This material was crystallized from ethyl acetate-ethyl ether to give the title compound (88 mg, 52% total yield) as fine white needles.

16330IK

mp 138-139.5°C (microhot stage);

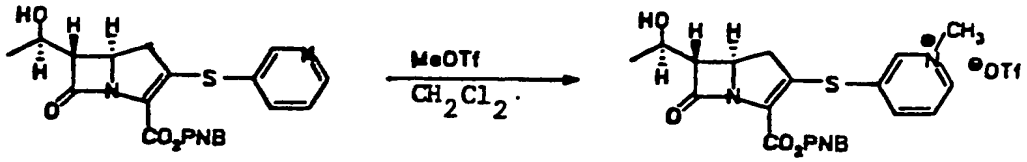
IR (Nujol) νmax 3540, 1765, 1705, 1520, 1350 cm^{-1};

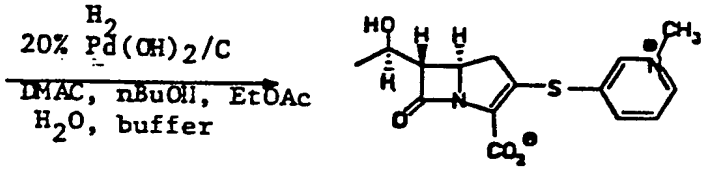
UV (dioxane) λ max 267 nm (ϵ13,380), 319 nm (ϵ15,050);

NMR ($CDCl_3$) δ 1.31 (d, J=6.2 Hz, $C\underline{H}_3CHOH$), 2.69 (m, CH_2), 3.14 (dd, J=2.8 and 6.6 Hz, H6), 4.15 (dt, J=2.8 and 9.1 Hz, H5), 4.21 (dq, J=6.5 Hz, $CH_3C\underline{H}OH$), 5.31 and 5.56 (two d, J=13.7 Hz, CH_2Ar), 7.36 (dd, J=4.8 and 8.0 Hz, pyridyl H5), 7.69 (d, J=8.8 Hz, 2ArH), 7.90 (ddd, J=1.4, 1.8 and 8.0 Hz, pyridyl H4), 8.25 (d, J=8.8 Hz, 2ArH), 8.69 (dd, J=1.4 and 4.8 Hz, pyridyl H6), 8.79 (d, J=1.8 Hz, pyridyl H2).

Anal. Calc'd for $C_{21}H_{19}N_3O_6S$:
C, 57.14; H, 4.34; N, 9.52; S, 7.26
Found: C, 56.65; H, 4.35; N, 9.34; S, 7.63.

STEP B:





(5R,6S)-6-[1(R)-Hydroxyethyl]-2-[(1-methyl-3-pyridinium)thio]carbapen-2-em-3-carboxylate

A solution of p-nitrobenzyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-(3-pyridylthio)carbapen-2-em-3-carboxylate (110.4 mg, 0.25 mmol) in anhydrous methylene chloride (2.5 ml) was cooled in an ice bath under a nitrogen atmosphere and treated with methyl trifluoromethanesulfonate (31 µl, 0.274 mmol). The mixture was stirred in the cold for 60 minutes. The solvent was decanted from the oily precipitate which

was washed with methylene chloride and dried under vacuum. The gummy residue was taken up in N,N-dimethylacetamide (2 ml), n-butanol (10 ml), ethyl acetate (5 ml), water (10 ml), and 0.5M pH 6.8 N-methylmorpholine-hydrochloric acid buffer (5 ml), treated with 20% palladium hydroxide on carbon (50 mg), and hydrogenated at 45 psi for 75 minutes. The mixture was filtered through celite to remove the catalyst which was washed with more water. The aqueous portion of the filtrate was washed with methylene chloride and ether, concentrated under vacuum to ca. 3 ml, and loaded onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 1.5 x 30 cm). The column was eluted with water in a cold room; 170 drop fractions were collected. Fractions 15-25 were combined, concentrated under vacuum to 15 ml, filtered through a 0.45 μ filter, and lyophilized to give the title compound (47 mg) as a yellow, amorphous powder.

IR (Nujol) ν max 1755, 1594 cm^{-1};

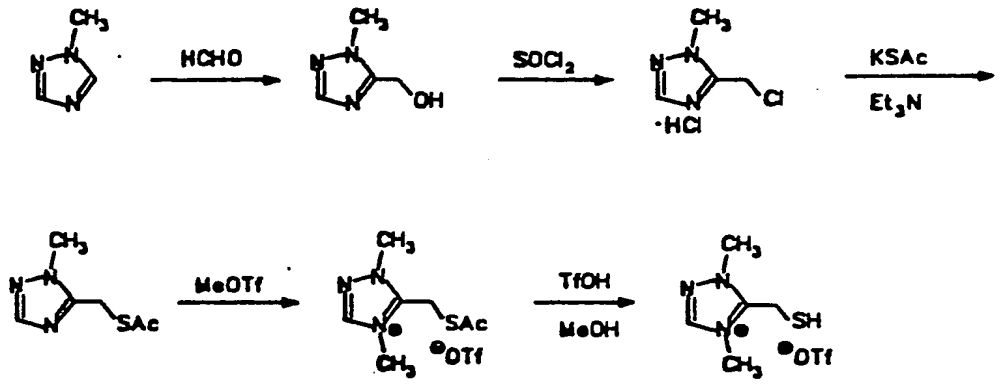
UV (0.05M pH 7.0 MOPS buffer) λ max 274 nm (ϵ7,710), 296 nm (ϵ8,240);

UV (buffer + $NH_2OH.HCl$) λ max 266 nm (ϵ 4,480), 316 nm (ϵ1,780) and extinguished λmax 296 nm (ϵ ext. 6,790);

NMR (D_2O) δ 1.25 (d, J=6.4 Hz, $C\underline{H}_3CHOH$), 2.80 (dd, J=9.9 and 17.5 Hz, $C\underline{H}_aH_b$), 2.94 (dd, J=8.5 and 17.5 Hz, $CH_a\underline{H}_b$), 3.45 (dd, J=2.9 and 5.9 Hz, H6), 4.23 (m, H5 and $CH_3C\underline{H}OH$), 4.41 (s, NCH_3), 8.04 (dd, J=6.0 and 8.2 Hz, pyridyl H5), 8.63 (br d, J=8.2 Hz, pyridyl H4), 8.78 (br d, J=6.0 Hz, pyridyl H6), 9.01 (br s, pyridyl H2).

EXAMPLE 9

STEPS A - E



1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate

Step A. 5-Hydroxymethyl-1-methyl-1,2,4-triazole

A solution of 1-methyl-1,2,4-triazole (4.16 g, 0.05 mol) in formalin (20 ml) was heated overnight in a sealed tube at 135°C. After cooling, the solvent was evaporated under vacuum to give a clear liquid that partially solidified on standing. This material was distilled to give a white, crystalline solid (4.65 g) bp. ca. 110°C/0.25 mm. The solid product was recrystallized from ethyl acetate-hexane to afford the title compound (3.78 g, 67%) as white crystals.

IR (Nujol) νmax 3180, 1505, 1290, 1200, 1045, 1000 cm^{-1};

NMR ($CDCl_3$) δ 3.95 (s, CH_3), 4.75 (d, J=6.5 Hz, CH_2), 5.49 (t, J=6.5 Hz, OH), 7.78 (s, H5);

Anal. Calc'd for $C_4H_7N_3O$:

C, 42.47; H, 6.24; N, 37.15

Found: C, 42.67; H, 6.16; N, 37.35.

Step B. 5-Chloromethyl-1-methyl-1,2,4-triazole hydrochloride

The hydroxymethyl triazole from Step 1 (1.00 g) was added to ice-cold thionyl chloride (4 ml) and the resulting mixture was heated at reflux for 25 minutes. Excess thionyl chloride was evaporated under vacuum. The solid residue was recrystallized from ethanol-ethyl acetate to give the title compound (1.17 g, 79% yield) as white crystals.

IR (Nujol) νmax 1585, 1400, 1265, 1250, 960 cm^{-1};
NMR (D_2O) δ 4.07 (s, CH_3), 4.85 (s, HOD), 5.04 (s, CH_2), 8.53 (s, H5);
Anal. Calc'd for $C_4H_7Cl_2N_3$:
C, 28.59; H, 4.20; N, 25.01
Found: C, 28.73; H, 4.16; N, 25.00.

Step C. 5-Acetylthiomethyl-1-methyl-1,2,4-triazole

A mixture of the chloromethyltriazole from Step 2 (609 mg, 3.63 mmol) and potassium thiolacetate (497 mg, 4.36 mmol) in anhydrous acetonitrile (7.3 ml) was treated with a speck of dicyclohexano-18-crown-6 and with triethylamine (531 µl, 3.81 mmol). The resulting mixture was stirred at room temperature for 3 hours. The mixture was filtered and the solids washed with acetonitrile. The filtrate and washings were evaporated under vacuum to a residue which was triturated with three portions of ethyl acetate. The ethyl acetate extracts were filtered, washed with brine, dried over magnesium sulfate, filtered, and evaporated under vacuum to afford the title compound (526 mg, 85%) as an orange liquid.
NMR ($CDCl_3$) δ 2.40 (s, CH_3CO), 3.91 (s, CH_3), 4.26 (s, CH_2), 7.80 (s, H5).

Step D. 5-Acetylthiomethyl-1,4-dimethyl-1,2,4-triazolium trifluoromethanesulfonate

A solution of 3-acetylthiomethyl-2-methyl-1,2,4-triazole (244 mg, 1.43 mmol) in anhydrous methylene chloride (1.4 ml) was cooled in an ice bath under a nitrogen atmosphere and treated with methyl trifluoromethanesulfonate (194 µl, 1.71 mmol). The resulting mixture was stirred in the cold for 30 minutes, then evaporated under vacuum. The residue was triturated three times with diethyl ether, then dissolved in anhydrous methylene chloride and evaporated under vacuum to afford the title compound (484 mg, 100%) as a viscous orange oil.

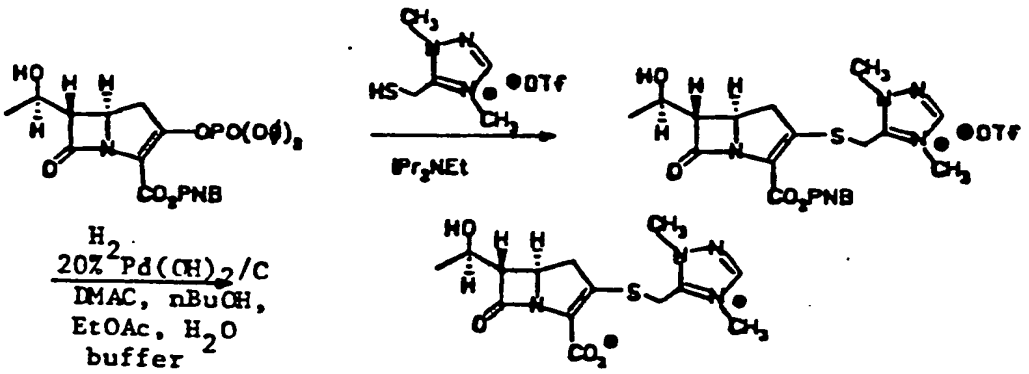
NMR (D_2O) δ 2.43 (s, CH_3CO), 3.95 (s, CH_3), 4.14 (s, CH_3), 4.62 (s, CH_2), 4.78 (s, HOD), 8.72 (s, H5).

StepE. 1,4-Dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate

A solution of the product from the preceding step (484 mg, 1.43 mmol) in anhydrous methanol (1.4 ml) was treated with trifluoromethanesulfonic acid (127 µl, 1.43 mmol) and kept at room temperature for 18.5 hours. The solution was diluted with ethyl ether to precipitate the product as an oil. The oil was washed four times with ethyl ether, diluted with anhydrous methylene chloride, and evaporated under vacuum to provide the title compound (344 mg, 82%) as a pale orange oil.

NMR (D_2O) δ 3.93 (s, CH_3), 4.08 (s, CH_3), 4.25 (s, CH_2), 4.78 (s, HOD), 8.72 (s, H5).

STEP F:



(5R,6S)-2-(1,4-Dimethyl-1,2,4-triazol-5-ium)methyl-thio-6-[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate

p-Nitrobenzyl (5R,6S)-2-(diphenylphosphono)-oxy-6-[1(R)-hydroxyethyl]carbapen-2-em-3-carboxylate (488 mg, 0.84 mmol) was added all at once to a solution of 1,4-dimethyl-5-mercaptomethyl-1,2,4-triazolium trifluoromethanesulfonate (370 mg, 1.26 mmol) in anhydrous N,N-dimethylacetamide which was cooled to -20°C under a nitrogen atmosphere. The resulting solution was treated dropwise over 7.5 minutes with a solution of N,N-diisopropylethylamine (220 µl, 1.26 mmol) in dimethylacetamide (0.4 ml) and stirred an additional 30 minutes at -20°C. The reaction mixture was diluted with n-butanol (40 ml), ethyl acetate (20 ml), water (40 ml) and 0.5M pH 6.8 N-methylmorpholine-hydrochloric acid buffer (20 ml), treated with 20% palladium hydroxide on carbon (250 mg), and hydrogenated at 45 psi for 90 minutes. The mixture was filtered through a celite pad to remove the catalyst which was washed with water. The aqueous portion of the filtrate was washed with methylene chloride (3x) and ethyl ether, concentrated under vacuum to ca. 20 ml, and loaded onto a column of Dowex 50W-X4 resin (sodium form, 200-400 mesh, 200 ml). The column was eluted with water in a cold

room; 400 drop fractions were collected every 4.6 minutes. Fractions 13-18 were concentrated under vacuum to 22 ml, filtered through a 0.45 μ CR acrodisc, and lyophilized to afford the title compound (121 mg) as a white amorphous solid.

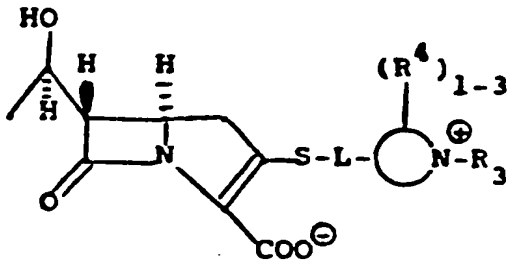
IR (Nujol) ν max 3320 (br), 1760, 1595, 1565, 1240 cm^{-1};

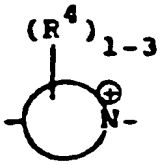
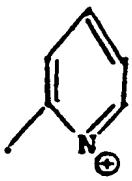
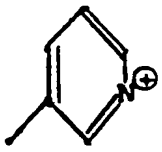
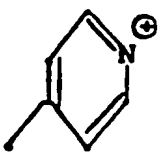
UV (0.05M pH 7.0 MOPS buffer) λmax 294 nm (98% NH_2OH extinguished, ϵ ext. 6,770);

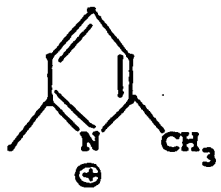
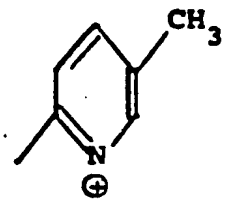
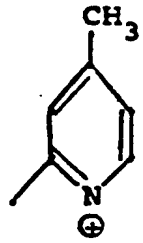
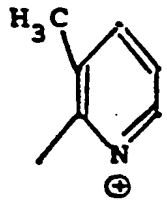
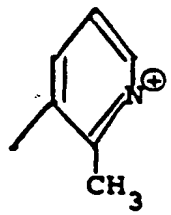
NMR (D_2O) δ 1.29 (d, J=6.4 Hz, $C\underline{H}_3CHOH$), 3.17 (dd, J=8.6 and 17.4 Hz, $CH_a\underline{H}_b$), 3.32 (dd, J=9.8 and 17.4 Hz, $CH_a\underline{H}_b$), 3.50 (dd, J=2.9 and 5.9 Hz, H6), 3.96 (s, NCH_3), 4.12 (s, NCH_3), 4.25 (m, H5 and $CH_3C\underline{H}OH$), 4.80 (s, HOD), 8.77 (s, triazolium H).

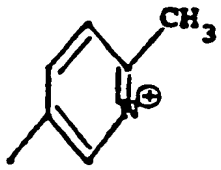
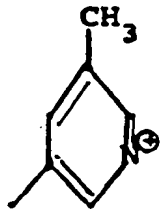
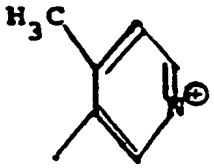
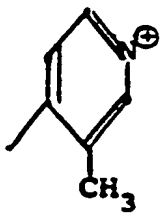
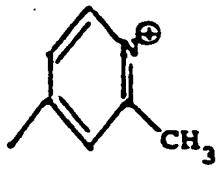
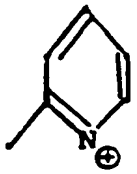
EXAMPLE 10

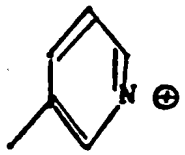
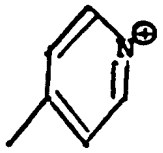
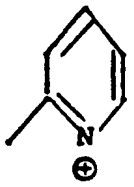
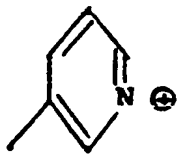
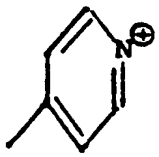
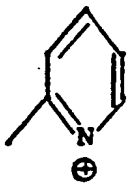
Utilizing the procedures of Examples 1-9 the following compounds are prepared:

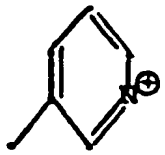
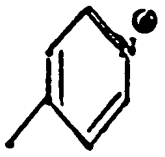
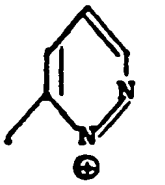
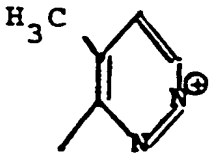
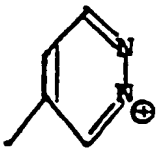
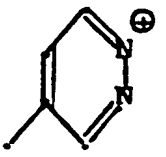


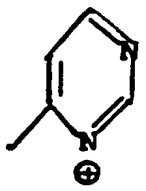
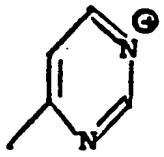
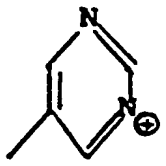
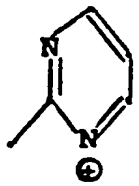
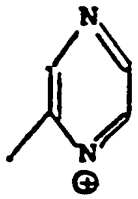
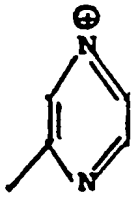
Compound No.	L		R^3
1	$-CH_2-$		$CH_2CH_2CH_3$
2	"	"	CH_2CH_3
3	"		$CH_2CH_2CH_3$
4	"	"	CH_2CH_3
5	"		$CH_2CH_2CH_3$

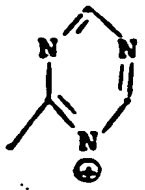
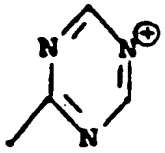
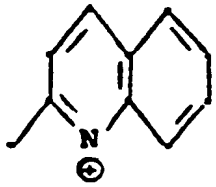
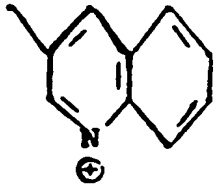
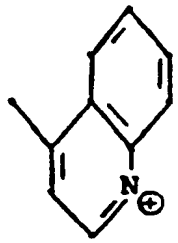
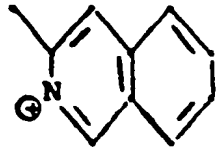
	6	$-CH_2-$	"	CH_2CH_3
	7	"		CH_3
	8	"		"
	9	"		"
	10	"		"
	11	"		"

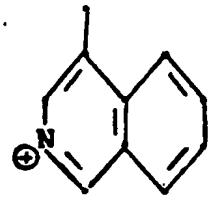
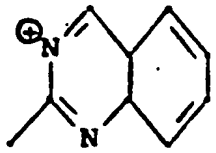
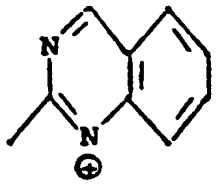
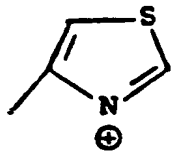
12	$-CH_2-$		CH_3	
13	"		"	
14	"		"	
15	"		"	
16	"		"	
17	$-CH_2CH_2-$		"	

18	$-CH_2CH_2-$		CH_3
19	"		"
20	$-CH-$ CH_3		"
21	"		"
22	"		"
23	$-CH_2-$		ϕCH_2

24	$-CH_2-$		ϕCH_2
25	"		"
26	"		CH_3
27	"		"
28	"		"
29	"		"

30	$-CH_2-$		CH_3
31	"		"
32	"		"
33	"		"
34	"		"
35	"		"

36	$-CH_2-$		CH_3
37	"		"
38	"		"
39	"		"
40	"		"
41	"		"

42	$-CH_2-$		CH_3
43	"		"
44	"		"
45	"		$CH_2CH_2CH_3$
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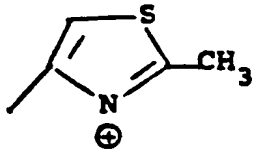
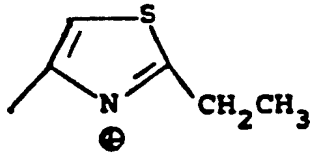
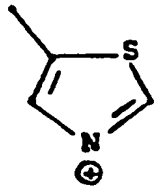
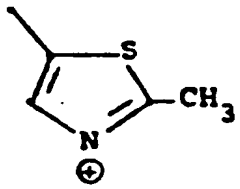
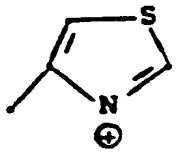
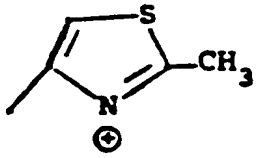
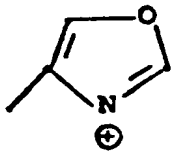
47	"		CH_3
48	"		"

49	$-CH_2-$		CH_3	
50	"		"	
51	$-CH-$ CH_3		"	
52	"		"	
53	$-CH_2-$		"	
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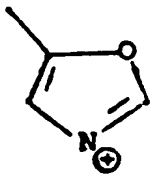
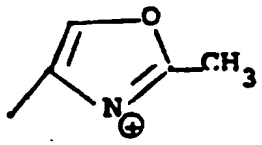
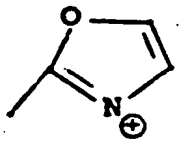
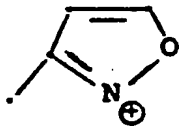
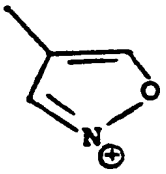
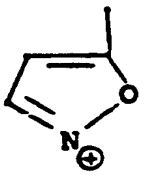
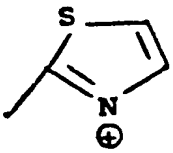
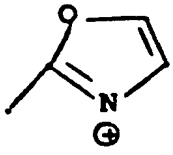
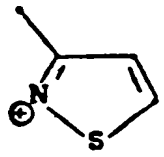
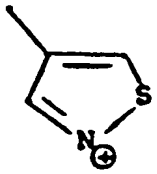
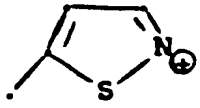
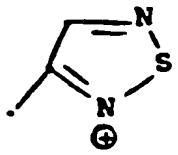
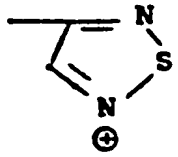
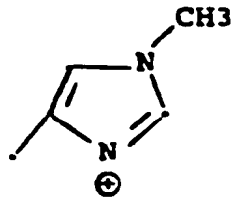
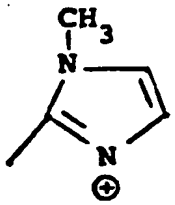
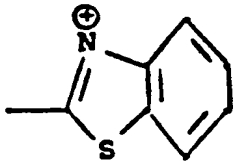
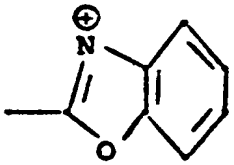
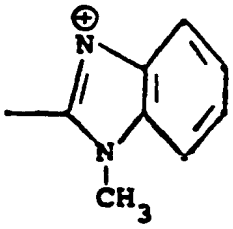
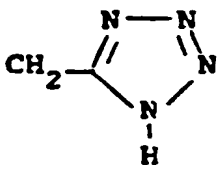
55	"		CH_3	

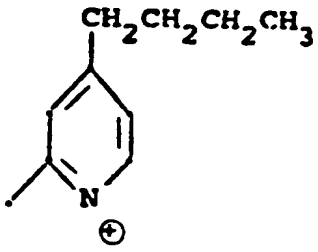
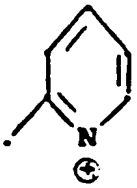
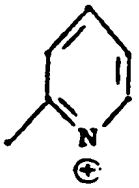
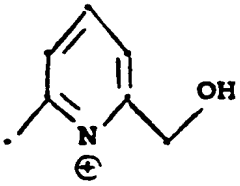
56	$-CH_2-$		CH_3	
57	"		"	
58	"		"	
59	"		"	
60	"		"	
61	"		"	
62	$-CH_2CH_2-$		"	

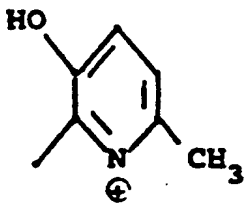
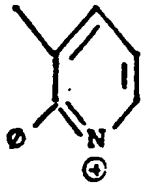
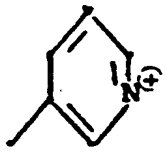
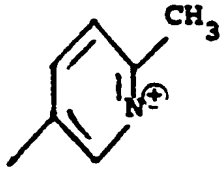
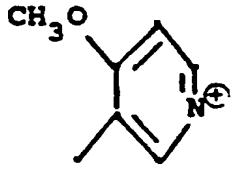
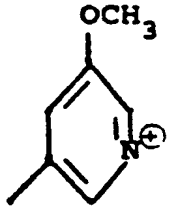
63	$-CH_2-$		CH_3
64	"		"
65	"		"
66	"		"
67	"		"
68	"		$-CH_2CH_2CH_3$
69	"	"	$-CH_2CH_3$

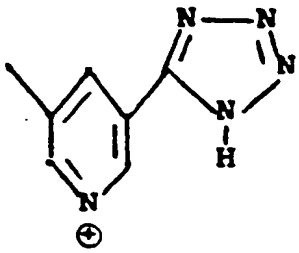
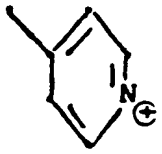
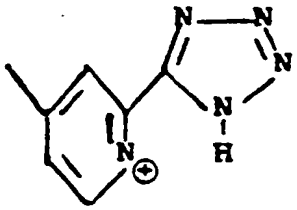
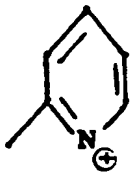
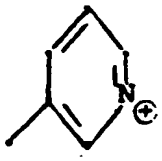
70	$-CH_2-$		$-CH_3$
71	"		"
72	"		"
73	"		"
74	"		CH_2OCH_3
75	"	"	CH_2CN
76	"	"	CH_2CO_2H
77	"	"	$CH_2SO_2CH_3$

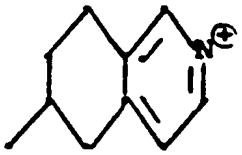
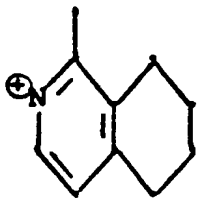
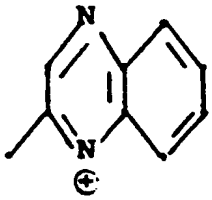
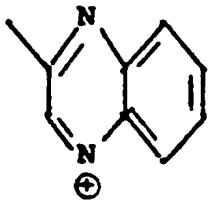
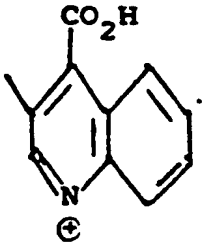
78	$-CH_2-$	"	$CH_2P(O)(OH)OCH_3$
79	"	"	CH_2SO_3H
80	"	"	CH_2CONMe_2
81	"	"	CH_2SOCH_3
82	"	"	CH_2NMe_2
83	"	"	
84	"		CH_2OCH_3
85	"	"	CH_2SCH_3
86	"	"	CH_2SOCH_3
87	"	"	$CH_2SO_2CH_3$
88	"	"	CH_2CO_2H
89	"	"	CH_2CONMe_2

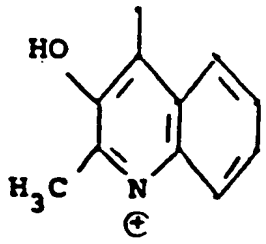
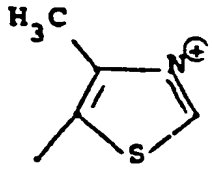
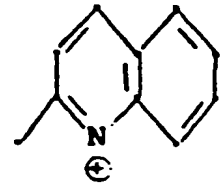
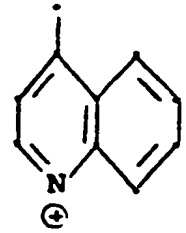
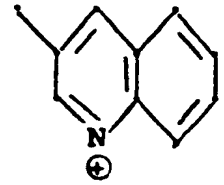
	90	$-CH_2-$	"	$CH_2P(O)(OH)OCH_3$
	91	"	"	CH_2SO_3H
	92	"	"	CH_2CN
	93	"	"	CH_2NMe_2
	94	"	"	$CH_2CH_2NMe_2$
	95	"		CH_2OCH_3
	96	"	"	CH_2NMe_2
	97	"	"	$CH_2CH_2NMe_2$
	98	"	"	CH_2CN
	99	"	"	CH_2SCH_3
	100	"	"	CH_2SOCH_3
	101	"	"	$CH_2SO_2CH_3$
	102	"	"	CH_2CO_2H
	103	"	"	CH_2CONMe_2

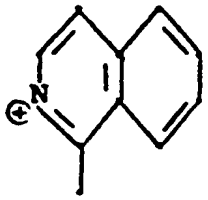
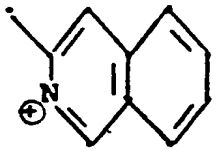
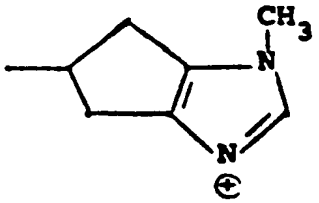
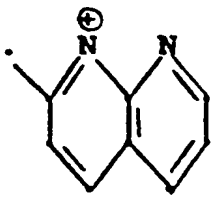
104	$-CH_2-$	"		$CH_2P(O)(OH)OCH_3$
105	"	"		CH_2SO_3H
106	"			CH_3
107	$-CH_2CH_2CH_2-$			"
108	$-CH_2CH(CH_2OH)-$			"
109	$-CH_2-$			"

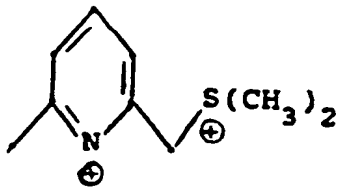
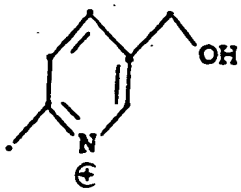
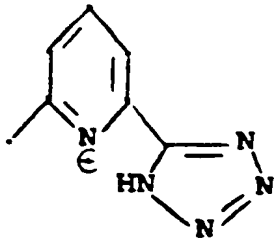
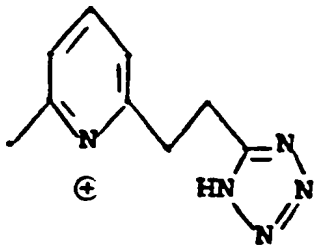
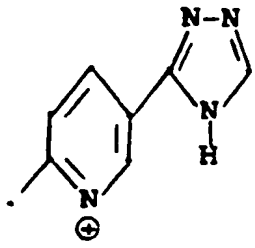
110	$-CH_2-$		CH_3	
111	"		"	
112	$-CH_2CH_2CH_2-$		"	
113	$-CH_2CH_2-$		"	
114	$-CH_2-$		"	
115	"		"	

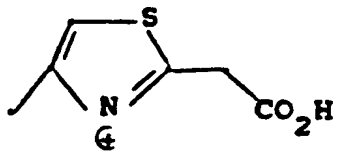
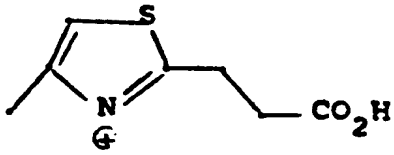
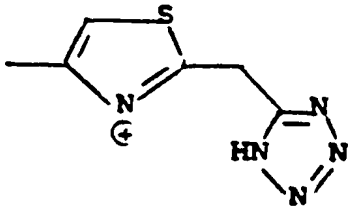
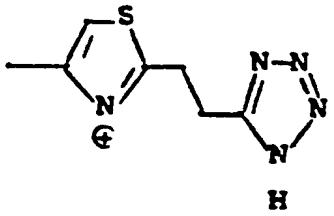
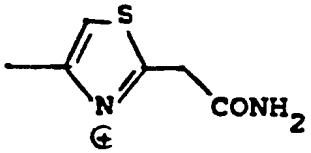
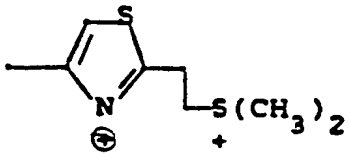
116	$-CH_2-$		CH_3
117	$-CH_2CH_2CH_2-$		"
118	CH_2		"
119	bond		"
120	"		CH_2CH_3
121	"		CH_2CH_3

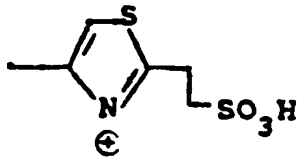
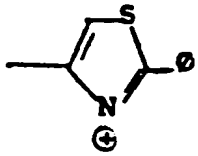
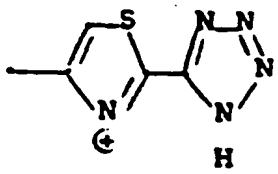
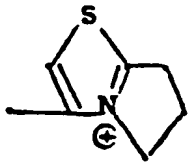
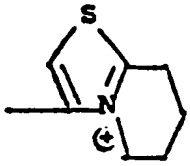
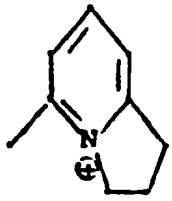
122	bond		CH_3
123	$-CH_2-$		"
124	"		"
125	"		"
126	"		"

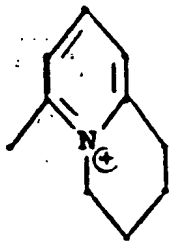
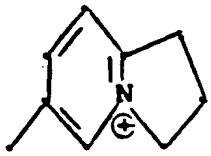
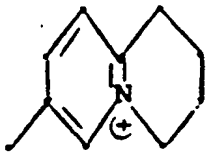
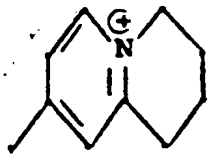
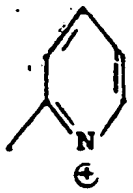
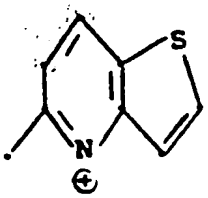
127	$-CH_2-$		CH_3
128	$-CH_2CH_2-$		"
129	bond		"
130	"		"
131	"		"

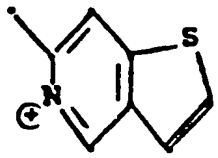
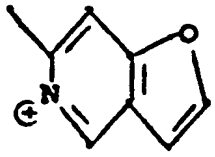
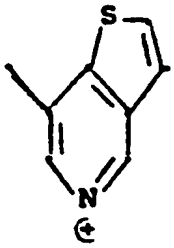
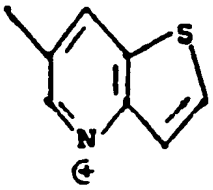
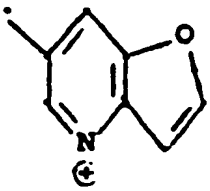
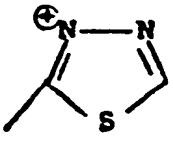
132	bond		CH_3	
133	"		"	
134	"		"	
135	"		"	
136	-CH- CH_3		"	

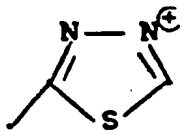
137	$-CH_2-$		CH_3	
138	"		"	
139	"		"	
140	"		"	
141	"		"	

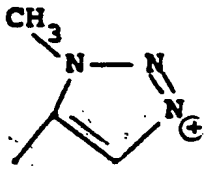
142	CH_2		CH_3	
143	"		"	
144	"		"	
145	"		"	
146	"		"	
147	"		"	

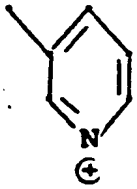
148	$-CH_2-$		CH_3	
149	"		"	
150	"		"	
151	"		--	
152	"		--	
153	"		--	

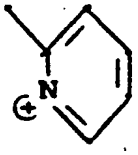
154	$-CH_2-$		--
155	"		-
156	"		--
157	"		--
158	$-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2-$		CH_3
159	$-CH_2-$		"

160	$-CH_2-$		CH_3
161	"		"
162	"		"
163	"		"
164	"		"
165	"		"

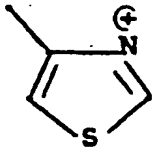
166 $-CH_2-$  CH_3

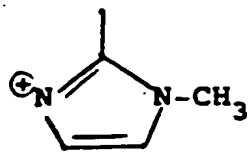
167 "  "

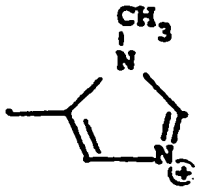
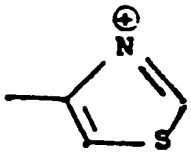
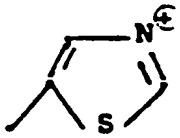
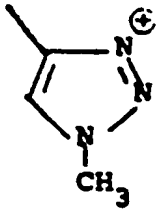
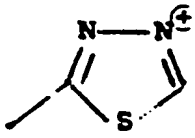
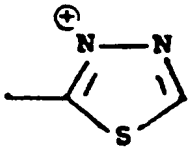
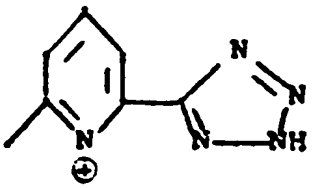
168 "  CH_2CONH_2

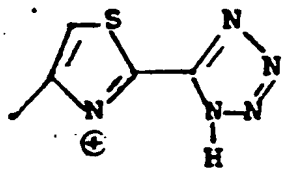
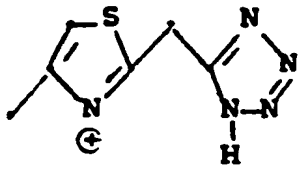
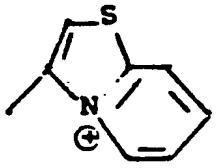
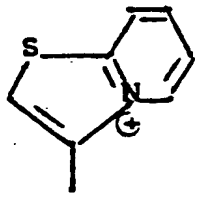
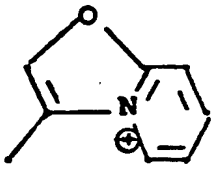
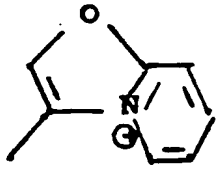
169 "  "

170 "  "

171 "  "

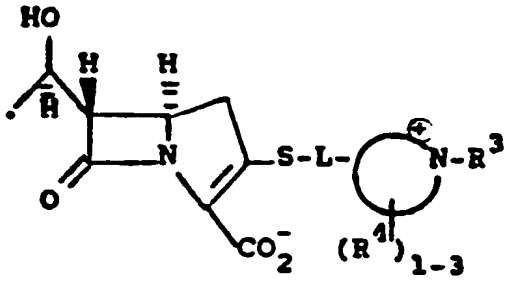
172 bond  CH_3

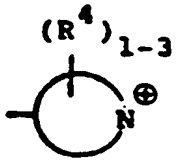
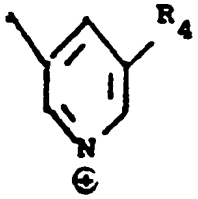
173	bond		CH_3
174	"		"
175	"		"
176	"		"
177	"		"
178	"		"
179	"		"

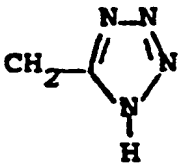
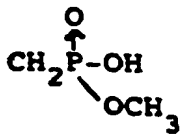
180	$-CH_2-$		CH_3
181	"		"
182	"		--
183	bond		--
184	CH_2		--
185	bond		--

EXAMPLE 11

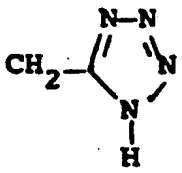
Utilizing the procedures of Examples 1-9, the following compounds are prepared:

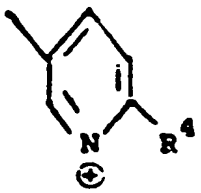


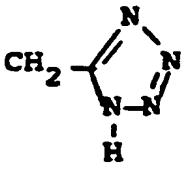
Compound No.	L		R_3	R_4
1	CH_2		CH_3	CO_2H
2	"	"	"	$CONH_2$
3	"	"	"	CN
4	"	"	"	OH
5	"	"	"	SO_2NH_2
6	"	"	"	SO_3H
7	"	"	"	NMe_2
8	"	"	"	$CONMe_2$

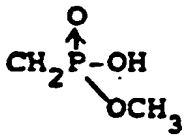
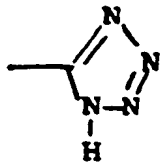
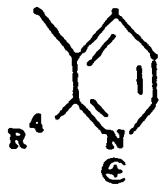
	9	"	"	"	CH_2NMe_2
	10	"	"	"	CH_2CN
	11	"	"	"	CH_2CONH_2
	12	"	"	"	CH_2CO_2H
	13	"	"	"	CH_2SCH_3
	14	"	"	"	CH_2SOCH_3
	15	"	"	"	$CH_2SO_2CH_3$
	16	"	"	"	SO_2CH_3
	17	"	"	"	$SOCH_3$
	18	"	"	"	
	19	"	"	"	$CH_2CH_2CO_2H$
	20	"	"	"	CH_2SO_3H
	21	"	"	"	CH_2OCH_3
	22	"	"	"	

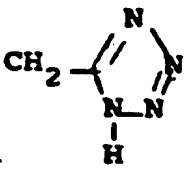
23	"	"	"	$CH_2CH_2SO_3H$
24	"	"	"	CF_3
25	"	"	"	$CH_2O\overset{O}{\overset{\|}{C}}NH_2$
26	"	"	"	$CH_2SO_2NH_2$
27	"	"	"	Br
28	"	"	"	Cl
29	"	"	"	F
30	"		"	CO_2H
31	"	"	"	$CONH_2$
32	"	"	"	CN
33	"	"	"	OH
34	"	"	"	$SONH_2$

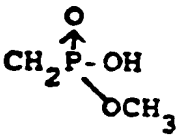
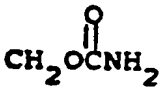
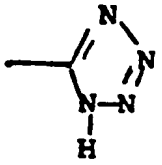
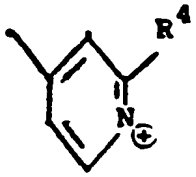
35	"	"	"	SO_3H
36	"	"	"	NMe_2
37	"	"	"	$CONMe_2$
38	"	"	"	CH_2NMe_2
39	"	"	"	CH_2CN
40	"	"	"	CH_2CONH_2
41	"	"	"	CH_2CO_2H
41	"	"	"	CH_2SCH_3
43	"	"	"	CH_2SOCH_3
44	"	"	"	$CH_2SO_2CH_3$
45	"	"	"	SO_2CH_3
46	"	"	"	$SOCH_3$
47	"	"	"	
48	"	"	"	$CH_2CH_2CO_2H$
49	"	"	"	CH_2SO_3H
50	"	"	"	CH_2OCH_3

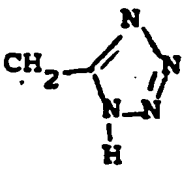
	51	"	"	"	$CH_2P(=O)(OH)OCH_3$
	52	"	"	"	$CH_2CH_2SO_3H$
	53	"	"	"	CF_3
	54	"	"	"	$CH_2OC(=O)NH_2$
	55	"	"	"	$CH_2SO_2NH_2$
	56	"	"	"	$CH_2SO_2NMe_2$
	57	"		"	CO_2H
	58	"	"	"	$CONH_2$
	59	"	"	"	CN
	60	"	"	"	OCH_3
	61	"	"	"	SO_2NH_2
	62	"	"	"	SO_3H
	63	"	"	"	NMe_2

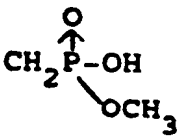
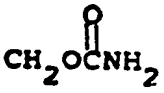
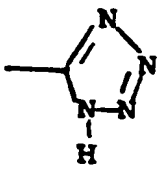
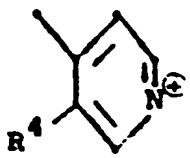
64	"	"	"	$CONMe_2$
65	"	"	"	CH_2NMe_2
66	"	"	"	CH_2CN
67	"	"	"	CH_2CONH_2
68	"	"	"	CH_2CO_2H
69	"	"	"	CH_2SCH_3
70	"	"	"	CH_2SOCH_3
71	"	"	"	$CH_2SO_2CH_3$
72	"	"	"	SO_2CH_3
73	"	"	"	$SOCH_3$
74	"	"	"	
75	"	"	"	$CH_2CH_2CO_2H$
76	"	"	"	CH_2SO_3H
77	"	"	"	CH_2OCH_3

78	"	"	"	
79	"	"	"	$CH_2CH_2SO_3H$
80	"	"	"	CF_3
81	"	"	"	CH_2OCNH_2 (O)
82	"	"	"	$CH_2SO_2NH_2$
83	"	"	"	$CH_2SO_2NMe_2$
84	"	"	"	
85	"		"	CO_2H
86	"	"	"	$CONH_2$
87	"	"	"	CN
88	"	"	"	OCH_3

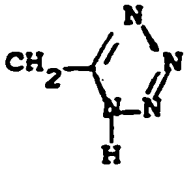
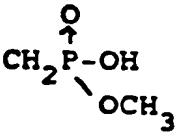
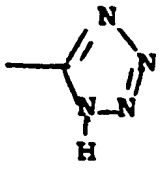
89	"	"	"	SO_2NH_2
90	"	"	"	SO_3H
91	"	"	"	NMe_2
92	"	"	"	$CONMe_2$
93	"	"	"	CH_2NMe_2
94	"	"	"	CH_2CN
95	"	"	"	CH_2CONH_2
96	"	"	"	CH_2CO_2H
97	"	"	"	CH_2SCH_3
98	"	"	"	CH_2SOCH_3
99	CH_3	"	"	$CH_2SO_2CH_3$
100	"	"	"	SO_2CH_3
101	"	"	"	$SOCH_3$
102	"	"	"	
103	"	"	"	$CH_2CH_2CO_2H$

104	"	"	"	CH_2SO_3H
105	"	"	"	CH_2OCH_3
106	"	"	"	
107	"	"	"	$CH_2CH_2SO_3H$
108	"	"	"	CF_3
109	"	"	"	
110	"	"	"	$CH_2SO_2NH_2$
111	"	"	"	$CH_2SO_2NMe_2$
112	"	"	"	
113	$-CH_2-$		"	CO_2H
114	"	"	"	$CONH_2$
115	"	"	"	CN

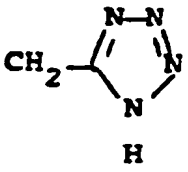
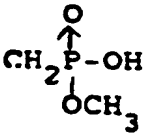
	116	"	"	"	OCH_3
	117	"	"	"	SO_2NH_2
	118	"	"	"	SO_3H
	119	"	"	"	NMe_2
	120	"	"	"	$CONMe_2$
	121	"	"	"	CH_2NMe_2
	122	"	"	"	CH_2CN
	123	"	"	"	CH_2CONH_2
	124	"	"	"	CH_2CO_2H
	125	"	"	"	CH_2SCH_3
	126	"	"	"	CH_2SOCH_3
	127	"	"	"	$CH_2SO_2CH_3$
	128	"	"	"	SO_2CH_3
	129	"	"	"	$SOCH_3$
	130	"	"	"	

131	"	"	"	$CH_2CH_2CO_2H$
132	"	"	"	CH_2SO_3H
133	"	"	"	CH_2OCH_3
134	"	"	"	
135	"	"	"	$CH_2CH_2SO_3H$
136	"	"	"	CF_3
137	"	"	"	
138	"	"	"	$CH_2SO_2NH_2$
139	"	"	"	$CH_2SO_2NMe_2$
140	"	"	"	
141	"		"	CO_2H
142	"	"	"	$CONH_2$

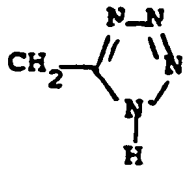
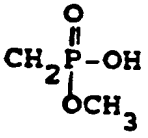
143	"	"	"	CN
144	"	"	"	OH
145	"	"	"	OCH_3
146	"	"	"	SO_2NH_2
147	"	"	"	SO_3H
148	"	"	"	NMe_2
149	"	"	"	$CONMe_2$
150	"	"	"	CH_2NMe_2
151	"	"	"	CH_2CN
152	"	"	"	CH_2CONH_2
153	"	"	"	CH_2CO_2H
154	"	"	"	CH_2SCH_3
155	"	"	"	CH_2SOCH_3
156	"	"	"	$CH_2SO_2CH_3$
157	"	"	"	SO_2CH_3
158	"	"	"	$SOCH_3$

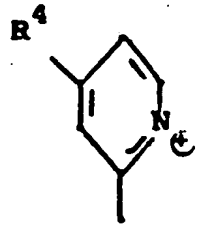
159	"	"	"	
160	"	"	"	$CH_2CH_2CO_2H$
161	"	"	"	CH_2SO_3H
162	"	"	"	CH_2OCH_3
163	"	"	"	
164	"	"	"	$CH_2CH_2SO_3H$
165	"	"	"	CF_3
166	"	"	"	CH_2OCNH_2
167	"	"	"	$CH_2SO_2NH_2$
168	"	"	"	$CH_2SO_2NMe_2$
169	"	"	"	

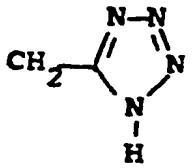
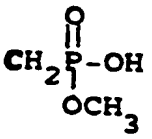
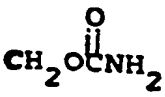
	170	"	"	"	F
	171	"	"	"	Cl
	172	"	"	"	Br
	173	"		"	CO_2H
	174	"	"	"	$CONH_2$
	175	"	"	"	CN
	176	"	"	"	SO_2NH_2
	177	"	"	"	SO_3H
	178	"	"	"	NMe_2
	179	"	"	"	$CONMe_2$
	180	"	"	"	CH_2NMe_2
	181	"	"	"	CH_2CN
	182	"	"	"	CH_2CONH_2
	183	"	"	"	CH_2CO_2H

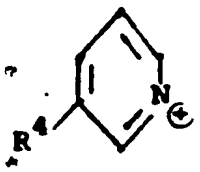
184	"	"	"	CH_2SCH_3
185	"	"	"	CH_2SOCH_3
186	"	"	"	$CH_2SO_2CH_3$
187	"	"	"	SO_2CH_3
188	"	"	"	
189	"	"	"	$CH_2CH_2CO_2H$
190	"	"	"	CH_2SO_3H
191	"	"	"	CH_2OCH_3
192	"	"	"	
193	"	"	"	$CH_2CH_2SO_3H$
194	"	"	"	CF_3
195	"	"	"	CH_2OCNH_2
196	"	"	"	$CH_2SO_2NH_2$

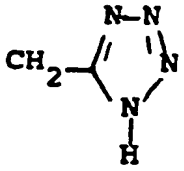
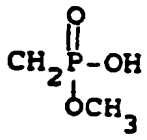
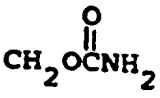
	197	"		"	CO_2H
	198	"	"	"	$CONH_2$
	199	"	"	"	CN
	200	"	"	"	OH
	201	"	"	"	SO_2NH_2
	202	"	"	"	SO_3H
	203	"	"	"	NMe_2
	204	"	"	"	$CONMe_2$
	205	"	"	"	CH_2NMe_2
	206	"	"	"	CH_2CN
	207	"	"	"	CH_2CONH_2
	208	"	"	"	CH_2CO_2H
	209	"	"	"	CH_2SCH_3
	210	"	"	"	CH_2SOCH_3

211	"	"	"	$CH_2SO_2CH_3$
212	"	"	"	SO_2CH_3
213	"	"	"	$SOCH_3$
214	"	"	"	
215	"	"	"	$CH_2CH_2CO_2H$
216	"	"	"	CH_2SO_3H
217	"	"	"	CH_2OCH_3
218	"	"	"	
219	"	"	"	$CH_2CH_2SO_3H$
220	"	"	"	CF_3
221	"	"	"	$CH_2O\overset{O}{\overset{\|}{C}}NH_2$
222	"	"	"	$CH_2SO_2NH_2$
223	"	"	"	Br

224	"	"	"	Cl
225	"	"	"	F
226	"		"	CO_2H
227	"	"	"	$CONH_2$
228	"	"	"	CN
229	"	"	"	SO_2NH_2
230	"	"	"	SO_3H
231	"	"	"	NMe_2
232	"	"	"	$CONMe_2$
233	"	"	"	CH_2NMe_2
234	"	"	"	CH_2CN
235	"	"	"	CH_2CONH_2
236	"	"	"	CH_2CO_2H
237	"	"	"	CH_2SCH_3

238	•	•	• CH_2SOCH_3
239	•	•	• $CH_2SO_2CH_3$
240	•	•	• SO_2CH_3
241	•	•	• $SOCH_3$
242	•	•	• 
243	•	•	• $CH_2CH_2CO_2H$
244	•	•	• CH_2SO_3H
245	•	•	• CH_2OCH_3
246	•	•	• 
247	•	•	• $CH_2CH_2SO_3H$
248	•	•	• CF_3
249	•	•	• 
250	•	•	• $CH_2SO_2NH_2$

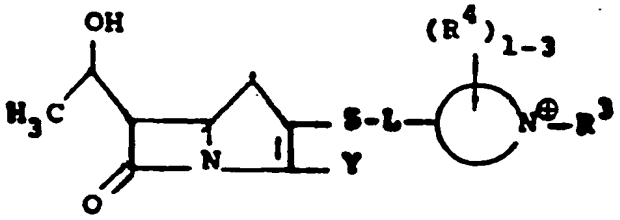
251	"		"	CO_2H
252	"	"	"	$CONH_2$
253	"	"	"	CN
254	"	"	"	OH
255	"	"	"	SO_2NH_2
256	"	"	"	SO_3H
257	"	"	"	NMe_2
258	"	"	"	$CONMe_2$
259	"	"	"	CH_2NMe_2
260	"	"	"	CH_2CN
261	"	"	"	CH_2CONH_2
262	"	"	"	CH_2CO_2H
263	"	"	"	CH_2SCH_3
264	"	"	"	CH_2SOCH_3

265	•	$CH_2SO_2CH_3$
266	•	SO_2CH_3
267	•	$SOCH_3$
268	•	
269	•	$CH_2CH_2CO_2H$
270	•	CH_2SO_3H
271	•	CH_2OCH_3
272	•	
273	•	$CH_2CH_2SO_3H$
274	•	CF_3
275	•	
276	•	$CH_2SO_2NH_2$

	277	"	"	" Br
	278	"	"	" Cl
	279	"	"	" F

WHAT IS CLAIMED IS:

1. A compound having the formula:



I

wherein:

L is a covalent bond or a bridging group selected from $-(CH_2)_{1-4}S-$; $-(CH_2)_{1-4}-O-$; $-(CH_2)_{1-4}-X-(CH_2)_{1-4}$ where X is O, S, NH, or $N(C_1-C_6)$alkyl); substituted or unsubstituted C_1-C_4 straight, C_1-C_6 branched or C_3-C_7 cycloalkyl groups wherein the substituents are selected from C_1-C_6 alkyl, $O-C_1-C_6$ alkyl, $S-C_1-C_6$ alkyl, halo, OH, CF_3, CN, NH_2, NHC_1-C_6 alkyl, $N(C_1-C_6$ alkyl$)_2$, CO_2H, $CONH_2$, $CONH(C_1-C_6$ alkyl), and $CON(C_1-C_6$ alkyl$)_2$;

is a mono- or bicyclic heteroarylium group containing from 5-11 ring atoms of which up to 5 are heteroatoms wherein R^3 is:

1) an unsubstituted or substituted C_1-C_6 alkyl radical;
2) an unsubstituted or substituted C_1-C_6 alkenyl radical;
3) an unsubstituted or substituted C_1-C_6 alkynyl radical;
4) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;
5) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;
6) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;
7) an unsubstituted or substituted bivalent C_2-C_6 alkylidene radical, optionally interrupted by a heteroatom, and joined to the heteroarylium group to form a ring which is carbocyclic or in which one or more atoms is replaced by a heteroatom. The new ring may contain one or more double bonds;
8) an unsubstituted or substituted phenyl or heteroaryl radical;
9) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical;
10) a cyano (C_1-C_4 alkyl) radical;

11) a carbamoyl (C_1-C_4 alkyl) radical;

12) a hydroxy (C_1-C_4 alkyl) radical;

13) an amino (C_1-C_4 alkyl) radical in which the nitrogen atom is unsubstituted or substituted with one to three C_1-C_4 alkyl groups;

14) an acidic side-chain of the structure $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

n = 0-4

m = 0-4

X = CHR^5, CH=CH, phenylene ($-C_6H_4-$), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, $CONH$, OCO_2, OC=O, NHC=O;

R^5 = H, O(C1-C4 alkyl), NH_2, NH(C1-C4 alkyl), N(C1-C4 alkyl)$_2$, CN, $CONH_2$, CON(C1-C4 alkyl)$_2$, CO_2H, SO_2NH_2, SO_2NH(C1-C4 alkyl);

Y = single bond, NH, N(C1-C4 alkyl), O, S;

A = an acidic function;

wherein the substituents in the above definitions of R^3 are independently selected from the group consisting of the definitions of R^4 set out below:

R^4 is independently selected from:

a) a trifluoromethyl group;

b) a halogen atom;

c) an unsubstituted or substituted C_1-C_4 alkoxyl radical;

d) a hydroxy group;

e) an unsubstituted or substituted (C_1-C_6 alkyl) carbonyloxy radical;

f) a carbamoyloxy radical which is unsubstituted or substituted on nitrogen with one or two C_1-C_4 alkyl groups;

g) a C_1-C_6 alkylthio radical, C_1-C_6 alkylsulfinyl radical or C_1-C_6 alkylsulfonyl radical, each of which is unsubstituted or substituted on the alkyl group;

h) a sulfamoyl group which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;

i) an amino group;

j) a mono (C_1-C_4 alkyl) amino or di(C_1-C_4 alkyl)amino group, each of which is unsubstituted or substituted on the alkyl group;

k) a formylamino group;

l) an unsubstituted or substituted (C_1-C_6 alkyl)carbonylamino radical;

m) a (C_1-C_4 alkoxyl) carbonylamino radical;

n) a ureido group in which the terminal nitrogen is unsubstituted or substituted with one or two C_1-C_4 alkyl groups;

o) a (C_1-C_6 alkyl) sulfonamido group;

p) a cyano group;

q) a formyl or acetalized formyl radical;

r) an unsubstituted or substituted (C_1-C_6 alkyl)carbonyl radical wherein the carbonyl is free or acetalized;

s) an unsubstituted or substituted phenylcarbonyl or heteroarylcarbonyl radical;

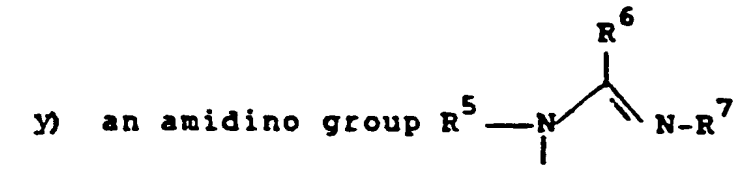
t) a hydroximinomethyl radical in which the oxygen or carbon atom is optionally substituted by a C_1-C_4 alkyl group;

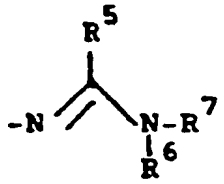
u) a (C_1-C_6 alkoxy)carbonyl radical;

v) a carbamoyl radical which is unsubstituted or substituted on nitrogen by one or two C_1-C_4 alkyl groups;

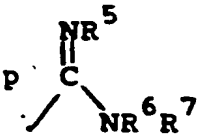
w) an N-hydroxycarbamoyl or N(C_1-C_4 alkoxy)carbamoyl radical in which the nitrogen atom may be additionally substituted by a C_1-C_4 alkyl group;

x) a thiocarbamoyl group;

y) an amidino group 



where R^5, R^6 and R^7 are independently hydrogen, C_1-C_4alkyl or wherein two of the alkyl groups together form a C_2-C_6alkylidene radical optionally interrupted by a heteroatom and joined together to form a ring;

z) a carboxamidino group  . where R^5, R^6 and R^7 are as defined above;

aa) a guanidinyl group where R^6 in y) above is NR^8R^9 and R^8 and R^9 are as defined for R^5 through R^7 above.

ab) hydrogen;

ac) an unsubstituted or substituted C_1-C_6 alkyl radical;

ad) an unsubstituted or substituted C_1-C_6 alkenyl radical;

ae) an unsubstituted or substituted C_1-C_6 alkynyl radical;

af) a C_3-C_7 cycloalkyl radical in which the ring is substituted or unsubstituted and one or more atoms may be replaced by a heteroatom;

ag) a C_3-C_7 cycloalkyl methyl radical in which the ring may be substituted and one or more atoms may be replaced by a heteroatom;

ah) an unsubstituted or substituted C_5-C_7 cycloalkenyl radical;

ai) an unsubstituted or substituted phenyl or heteroaryl radical;

aj) an unsubstituted or substituted phenyl (C_1-C_4 alkyl) or heteroaryl (C_1-C_4 alkyl) radical; and

ak) an acidic side chain of the structure
-A or $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

n = 0-4

m = 0-4

X = CHR^s, CH=CH, phenylene ($-C_6H_4-$), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;

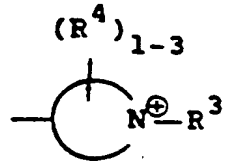
R^s = H, O(C1-C4 alkyl), NH_2, NH(C1-C4 alkyl), $N(C1\text{-}C4\ alkyl)_2$, CN, $CONH_2$, $CON(C1\text{-}C4\ alkyl)_2$, CO_2H, SO_2NH_2, $SO_2NH(C1\text{-}C4\ alkyl)$;

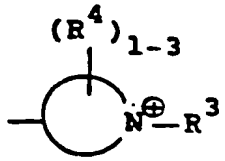
Y = single bond, NH, N(C1-C4 alkyl), O, S;

A = an acidic function

Y is selected from: i) COOH or a pharmaceutically acceptable ester or salt thereof, ii) $COOR^1$ wherein R^1 is a removable carboxy protecting group, iii) COOM wherein M is an alkali metal, or iv) $COO^{\ominus}$; provided that when Y is other than iv) a counterion $Z^{\ominus}$ is provided.

2. A compound of Claim 1 wherein L is substituted or unsubstituted branched or linear C_1-C_4 alkyl.

3. A compound of Claim 2 wherein  is monocyclic heteroarylium.

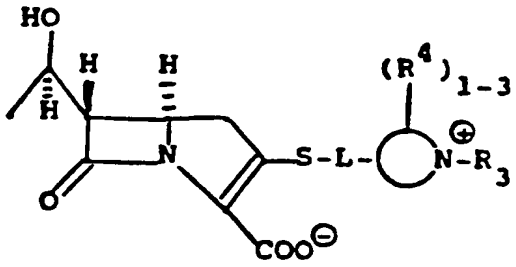
4. A compound of Claim 3 wherein  is a pyridinium group.

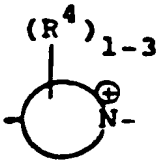
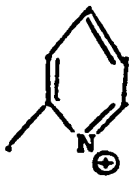
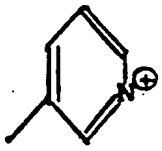
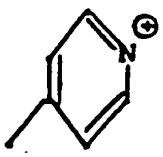
5. A compound of Claim 4 wherein R^3 is an unsubstituted or substituted C_1-C_4 alkyl group.

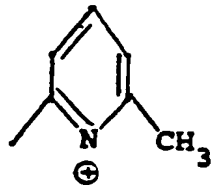
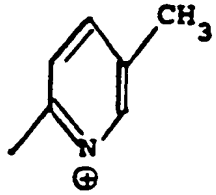
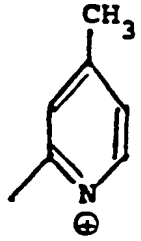
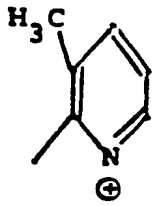
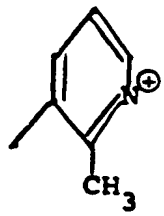
6. A compound of Claim 5 wherein L is

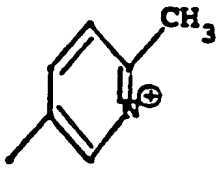
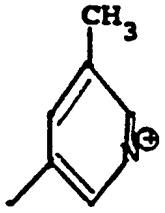
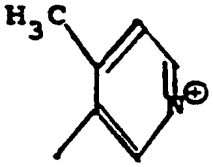
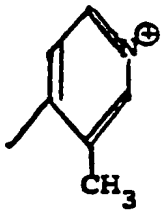
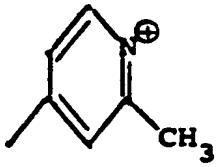
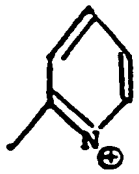
$-CH_2-$,
$-CH(CH_3)-$ or $-(CH_2)_2-$.

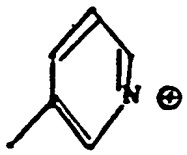
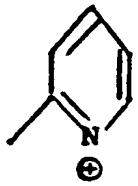
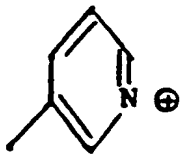
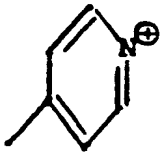
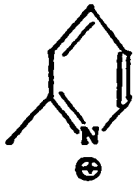
7. A compound of Claim 1 wherein the compound is a member selected from the group consisting of:

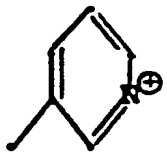
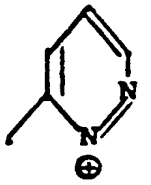
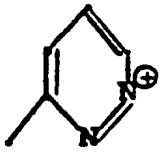
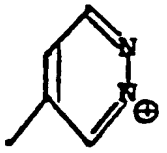
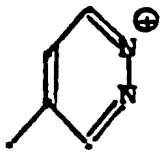


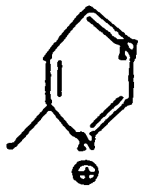
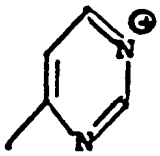
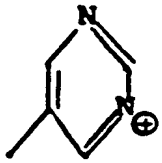
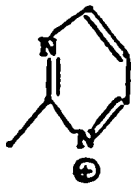
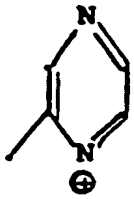
Compound No.	L		R^3
1	$-CH_2-$		$CH_2CH_2CH_3$
2	"	"	CH_2CH_3
3	"		$CH_2CH_2CH_3$
4	"	"	CH_2CH_3
5	"		$CH_2CH_2CH_3$

6	$-CH_2-$	"		CH_2CH_3
7	"			CH_3
8	"			"
9	"			"
10	"			"
11	"			"

12	$-CH_2-$		CH_3	
13	"		"	
14	"		"	
15	"		"	
16	"		"	
17	$-CH_2CH_2-$		"	

18	$-CH_2CH_2-$		CH_3
19	"		"
20	$-CH-$ CH_3		"
21	"		"
22	"		"
23	$-CH_2-$		$\varnothing CH_2$

24	$-CH_2-$		$\emptyset CH_2$
25	"		"
26	"		CH_3
27	"		"
28	"		"
29	"		"

30	$-CH_2-$		CH_3	
31	"		"	
32	"		"	
33	"		"	
34	"		"	
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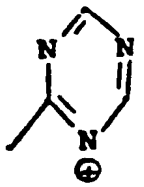
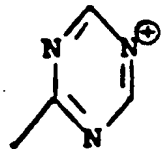
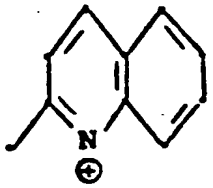
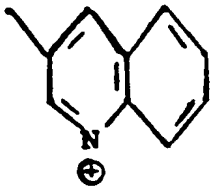
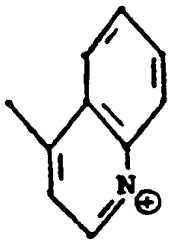
36	$-CH_2-$		CH_3
37	"		"
38	"		"
39	"		"
40	"		"
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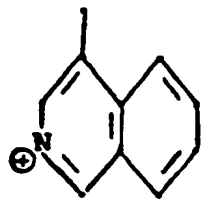
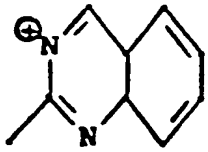
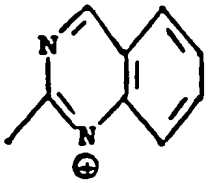
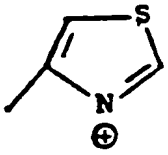
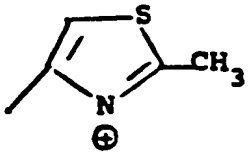
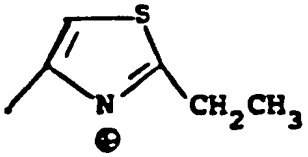
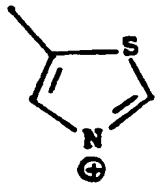
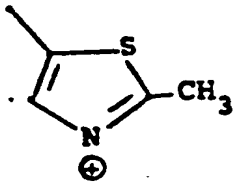
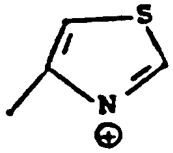
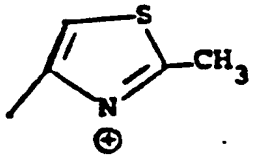
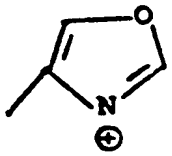
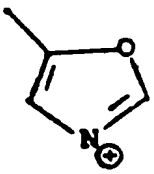
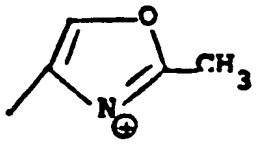
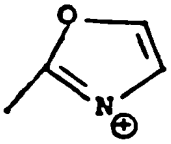
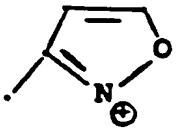
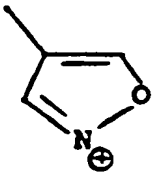
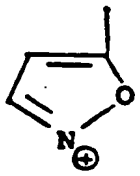
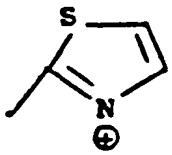
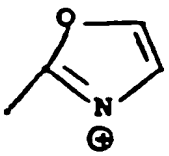
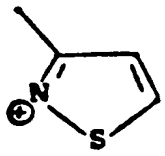
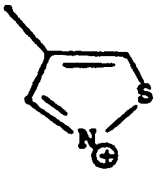
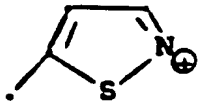
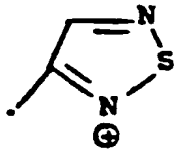
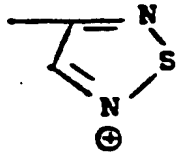
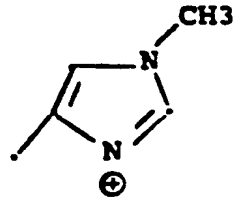
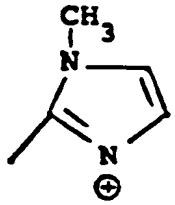
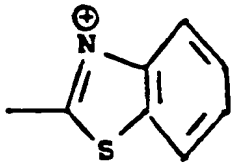
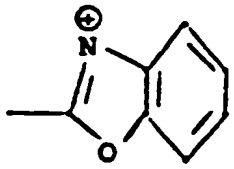
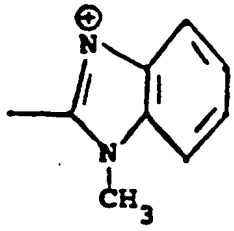
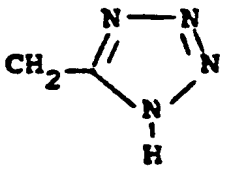
42	$-CH_2-$		CH_3
43	"		"
44	"		"
45	"		$CH_2CH_2CH_3$
46	"	"	CH_2CH_3
47	"		CH_3
48	"		"

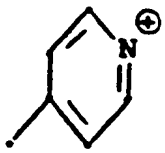
49	$-CH_2-$		CH_3
50	"		"
51	$-CH-$ CH_3		"
52	"		"
53	$-CH_2-$		"
54	"	"	CH_2CH_3
55	"		CH_3

56	$-CH_2-$		CH_3	CH_3
57	"		"	"
58	"		"	"
59	"		"	"
60	"		"	"
61	"		"	"
62	$-CH_2CH_2-$		"	"

63	$-CH_2-$		CH_3
64	"		"
65	"		"
66	"		"
67	"		"
68	"		$-CH_2CH_2CH_3$
69	"	"	$-CH_2CH_3$

70	$-CH_2-$		$-CH_3$
71	"		"
72	"		"
73	"		"
74	"		CH_2OCH_3
75	"	"	CH_2CN
76	"	"	CH_2CO_2H
77	"	"	$CH_2SO_2CH_3$

78	$-CH_2-$	"	$CH_2P(O)(OH)OCH_3$
79	"	"	CH_2SO_3H
80	"	"	CH_2CONMe_2
81	"	"	CH_2SOCH_3
82	"	"	CH_2NMe_2
83	"	"	
84	"		CH_2OCH_3
85	"	"	CH_2SCH_3
86	"	"	CH_2SOCH_3
87	"	"	$CH_2SO_2CH_3$
88	"	"	CH_2CO_2H
89	"	"	CH_2CONMe_2

90	$-CH_2-$	"		$CH_2P(O)(OH)OCH_3$
91	"	"		CH_2SO_3H
92	"	"		CH_2CN
93	"	"		CH_2NMe_2
94	"	"		$CH_2CH_2NMe_2$
95	"			CH_2OCH_3
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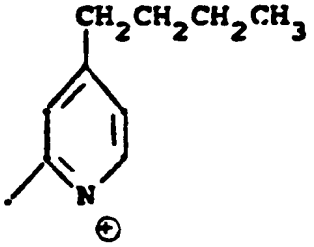
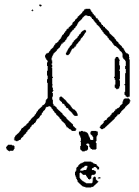
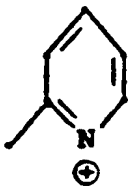
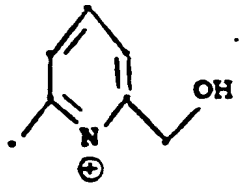
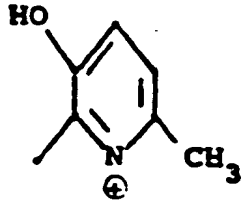
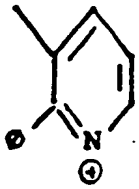
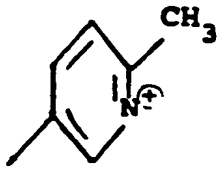
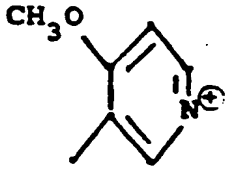
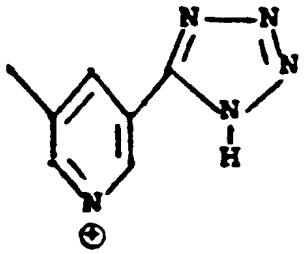
97	"	"		$CH_2CH_2NMe_2$
98	"	"		CH_2CN
99	"	"		CH_2SCH_3
100	"	"		CH_2SOCH_3
101	"	"		$CH_2SO_2CH_3$
102	"	"		CH_2CO_2H
103	"	"		CH_2CONMe_2

104	$-CH_2-$	"		$CH_2P(O)(OH)OCH_3$
105	"	"		CH_2SO_3H
106	"			CH_3
107	$-CH_2CH_2CH_2-$			"
108	$-CH_2CH(CH_2OH)-$			"
109	$-CH_2-$			"

110	$-CH_2-$		CH_3	
111	"		"	
112	$-CH_2CH_2CH_2-$		"	
113	$-CH_2CH_2-$		"	
114	$-CH_2-$		"	
115	"		"	

116	$-CH_2-$		CH_3
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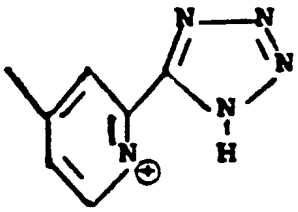
118	CH_2		"
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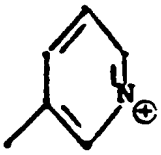
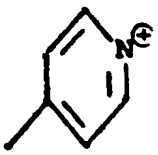
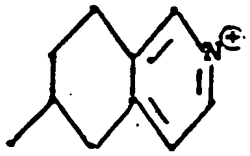
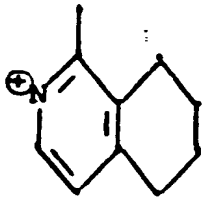
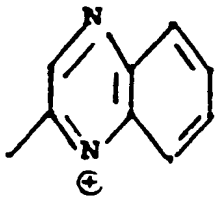
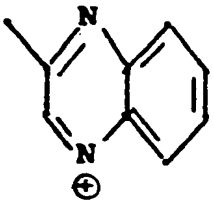
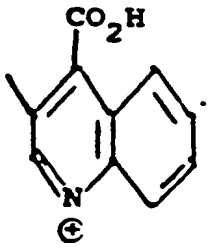
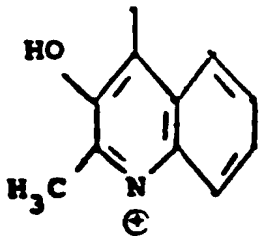
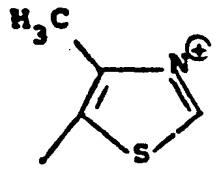
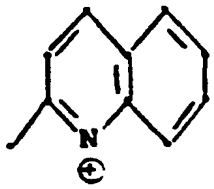
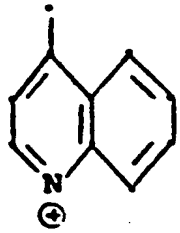
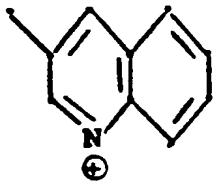
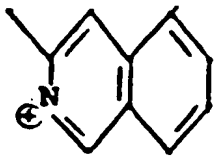
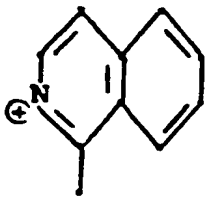
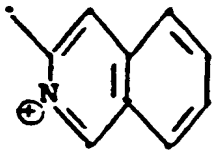
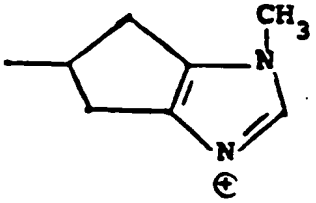
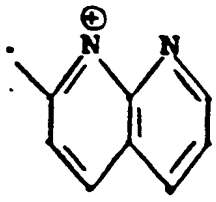
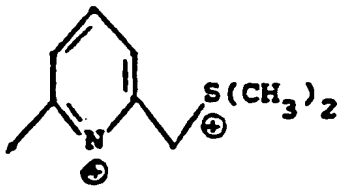
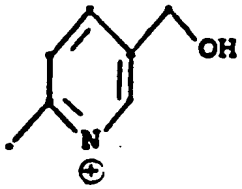
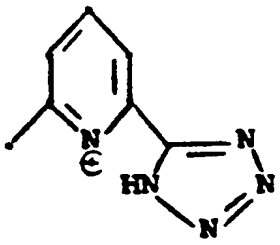
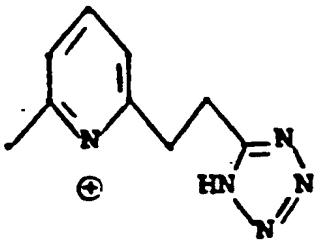
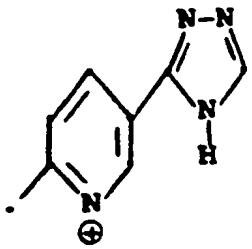
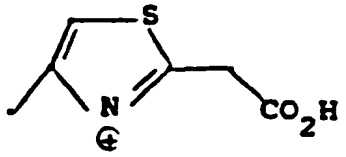
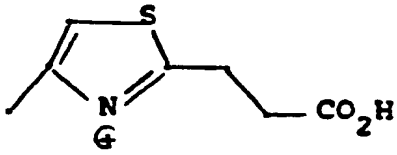
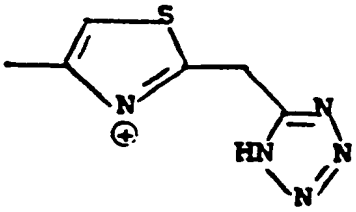
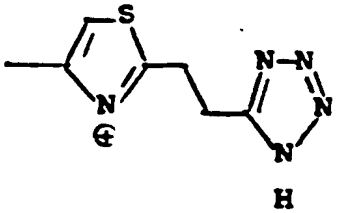
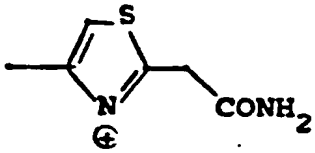
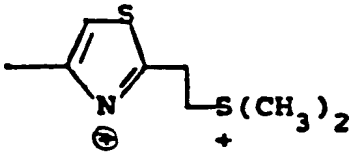
120	"		"
121	"		CH_2CH_3

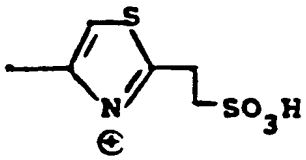
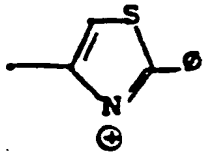
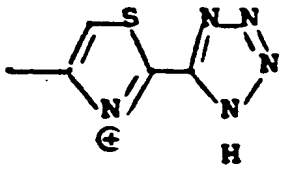
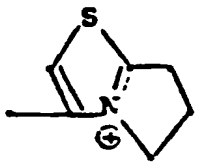
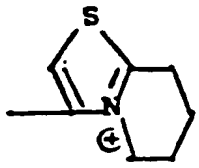
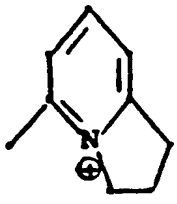
122	bond		CH_3
123	$-CH_2-$		"
124	"		"
125	"		"
126	"		"

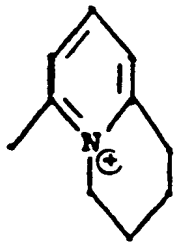
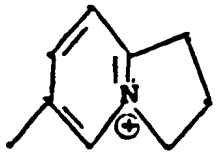
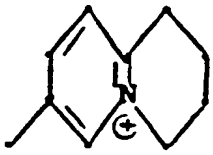
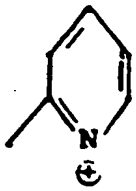
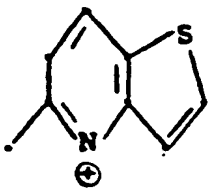
127	$-CH_2-$		CH_3	
128	$-CH_2CH_2-$		"	
129	bond		"	
130	"		"	
131	"		"	

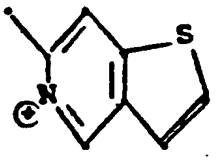
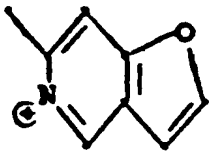
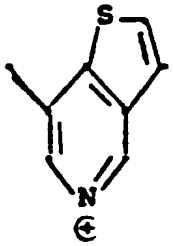
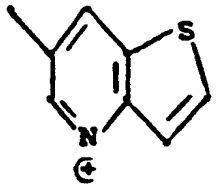
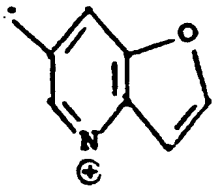
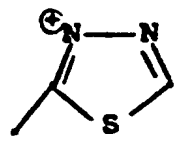
132	bond		CH_3
133	"		"
134	"		"
135	"		"
136	$-CH-$ CH_3		"

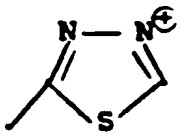
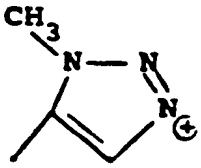
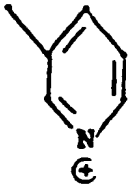
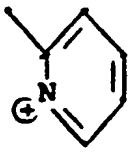
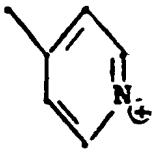
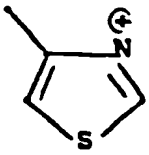
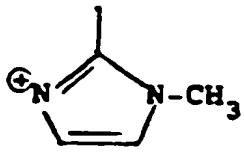
137	$-CH_2-$		CH_3	
138	"		"	
139	"		"	
140	"		"	
141	"		"	

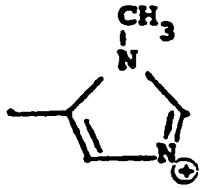
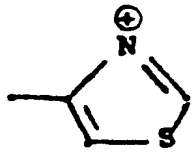
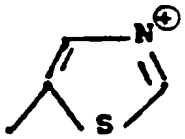
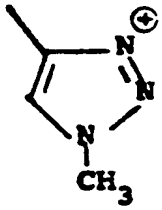
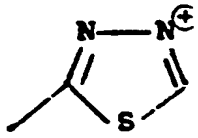
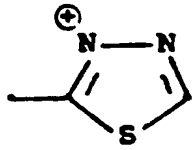
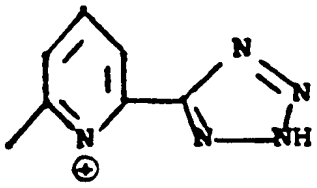
142	CH_2		CH_3	
143	"		"	
144	"		"	
145	"		"	
146	"		"	
147	"		"	

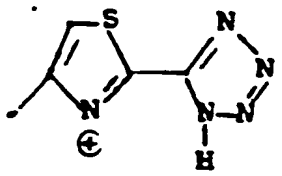
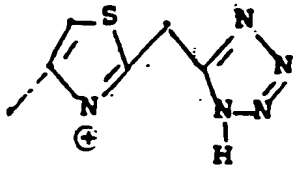
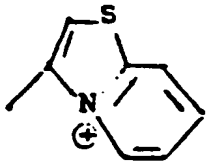
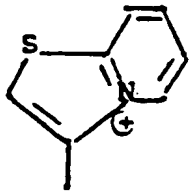
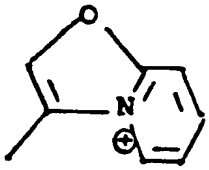
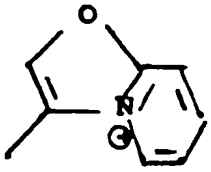
148	$-CH_2-$		CH_3	
149	"		"	
150	"		"	
151	"		--	
152	"		--	
153	"		--	

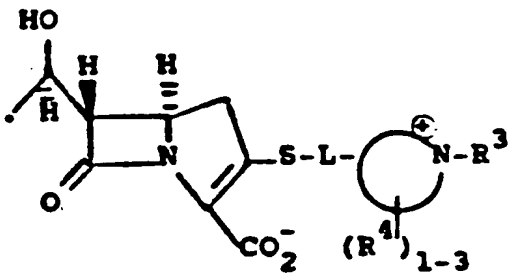
154	$-CH_2-$		--
155	"		-
156	"		--
157	"		--
158	$-\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2-$		CH_3
159	$-CH_2-$		"

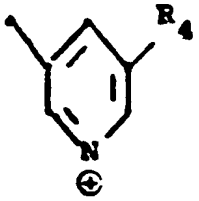
160	$-CH_2-$		CH_3
161	"		"
162	"		"
163	"		"
164	"		"
165	"		"

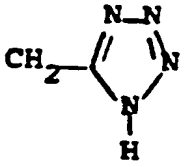
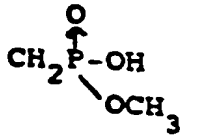
166	$-CH_2-$		CH_3
167	"		"
168	"		CH_2CONH_2
169	"		"
170	"		"
171	"		"
172	bond		CH_3

173	bond		CH_3
174	"		"
175	"		"
176	"		"
177	"		"
178	"		"
179	"		"

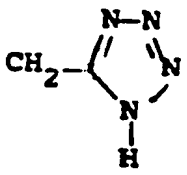
180	$-CH_2-$		CH_3	
181	"		"	
182	"		--	
183	bond		--	
184	CH_2		--	
185	bond		--	

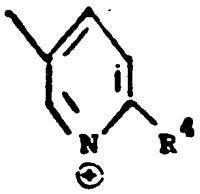


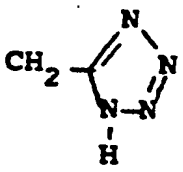
Compound No.	L	$(R^4)_{1-3}$	R_3	R_4
1	CH_2		CH_3	CO_2H
2	"	"	"	$CONH_2$
3	"	"	"	CN
4	"	"	"	OH
5	"	"	"	SO_2NH_2
6	"	"	"	SO_3H
7	"	"	"	NMe_2
8	"	"	"	$CONMe_2$

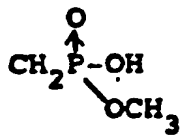
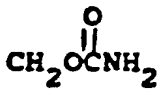
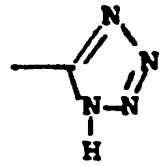
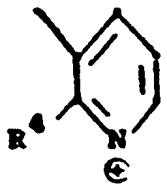
9	"	"	"	CH_2NMe_2
10	"	"	"	CH_2CN
11	"	"	"	CH_2CONH_2
12	"	"	"	CH_2CO_2H
13	"	"	"	CH_2SCH_3
14	"	"	"	CH_2SOCH_3
15	"	"	"	$CH_2SO_2CH_3$
16	"	"	"	SO_2CH_3
17	"	"	"	$SOCH_3$
18	"	"	"	
19	"	"	"	$CH_2CH_2CO_2H$
20	"	"	"	CH_2SO_3H
21	"	"	"	CH_2OCH_3
22	"	"	"	

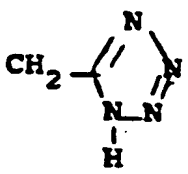
23	"	"	"	$CH_2CH_2SO_3H$
24	"	"	"	CF_3
25	"	"	"	$CH_2O\overset{O}{\overset{\|}{C}}NH_2$
26	"	"	"	$CH_2SO_2NH_2$
27	"	"	"	Br
28	"	"	"	Cl
29	"	"	"	F
30	"		"	CO_2H
31	"	"	"	$CONH_2$
32	"	"	"	CN
33	"	"	"	OH
34	"	"	"	$SONH_2$

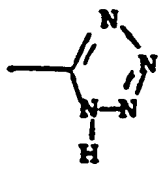
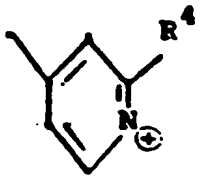
35	"	"	"	SO_3H
36	"	"	"	NMe_2
37	"	"	"	$CONMe_2$
38	"	"	"	CH_2NMe_2
39	"	"	"	CH_2CN
40	"	"	"	CH_2CONH_2
41	"	"	"	CH_2CO_2H
41	"	"	"	CH_2SCH_3
43	"	"	"	CH_2SOCH_3
44	"	"	"	$CH_2SO_2CH_3$
45	"	"	"	SO_2CH_3
46	"	"	"	$SOCH_3$
47	"	"	"	
48	"	"	"	$CH_2CH_2CO_2H$
49	"	"	"	CH_2SO_3H
50	"	"	"	CH_2OCH_3

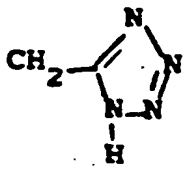
	51	"	"	"	$CH_2P(=O)(OH)OCH_3$
	52	"	"	"	$CH_2CH_2SO_3H$
	53	"	"	"	CF_3
	54	"	"	"	CH_2OCNH_2 (O)
	55	"	"	"	$CH_2SO_2NH_2$
	56	"	"	"	$CH_2SO_2NMe_2$
	57	"		"	CO_2H
	58	"	"	"	$CONH_2$
	59	"	"	"	CN
	60	"	"	"	OCH_3
	61	"	"	"	SO_2NH_2
	62	"	"	"	SO_3H
	63	"	"	"	NMe_2

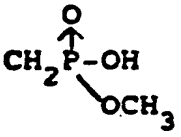
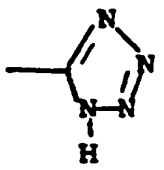
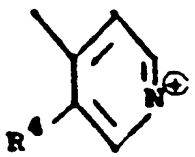
64	"	"	"	$CONMe_2$
65	"	"	"	CH_2NMe_2
66	"	"	"	CH_2CN
67	"	"	"	CH_2CONH_2
68	"	"	"	CH_2CO_2H
69	"	"	"	CH_2SCH_3
70	"	"	"	CH_2SOCH_3
71	"	"	"	$CH_2SO_2CH_3$
72	"	"	"	SO_2CH_3
73	"	"	"	$SOCH_3$
74	"	"	"	
75	"	"	"	$CH_2CH_2CO_2H$
76	"	"	"	CH_2SO_3H
77	"	"	"	CH_2OCH_3

	78	"	"	"	
	79	"	"	"	$CH_2CH_2SO_3H$
	80	"	"	"	CF_3
	81	"	"	"	
	82	"	"	"	$CH_2SO_2NH_2$
	83	"	"	"	$CH_2SO_2NMe_2$
	84	"	"	"	
	85	"		"	CO_2H
	86	"	"	"	$CONH_2$
	87	"	"	"	CN
	88	"	"	"	OCH_3

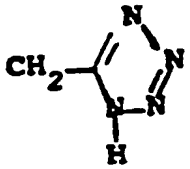
89	"	"	"	SO_2NH_2
90	"	"	"	SO_3H
91	"	"	"	NMe_2
92	"	"	"	$CONMe_2$
93	"	"	"	CH_2NMe_2
94	"	"	"	CH_2CN
95	"	"	"	CH_2CONH_2
96	"	"	"	CH_2CO_2H
97	"	"	"	CH_2SCH_3
98	"	"	"	CH_2SOCH_3
99	CH_3	"	"	$CH_2SO_2CH_3$
100	"	"	"	SO_2CH_3
101	"	"	"	$SOCH_3$
102	"	"	"	
103	"	"	"	$CH_2CH_2CO_2H$

104	"	"	"	CH_2SO_3H
105	"	"	"	CH_2OCH_3
106	"	"	"	$CH_2P(=O)(OH)OCH_3$
107	"	"	"	$CH_2CH_2SO_3H$
108	"	"	"	CF_3
109	"	"	"	$CH_2OC(=O)NH_2$
110	"	"	"	$CH_2SO_2NH_2$
111	"	"	"	$CH_2SO_2NMe_2$
112	"	"	"	
113	$-CH_2-$		"	CO_2H
114	"	"	"	$CONH_2$
115	"	"	"	CN

	116	"	"	"	OCH_3
	117	"	"	"	SO_2NH_2
	118	"	"	"	SO_3H
	119	"	"	"	NMe_2
	120	"	"	"	$CONMe_2$
	121	"	"	"	CH_2NMe_2
	122	"	"	"	CH_2CN
	123	"	"	"	CH_2CONH_2
	124	"	"	"	CH_2CO_2H
	125	"	"	"	CH_2SCH_3
	126	"	"	"	CH_2SOCH_3
	127	"	"	"	$CH_2SO_2CH_3$
	128	"	"	"	SO_2CH_3
	129	"	"	"	$SOCH_3$
	130	"	"	"	

131	"	"	"	$CH_2CH_2CO_2H$
132	"	"	"	CH_2SO_3H
133	"	"	"	CH_2OCH_3
134	"	"	"	
135	"	"	"	$CH_2CH_2SO_3H$
136	"	"	"	CF_3
137	"	"	"	
138	"	"	"	$CH_2SO_2NH_2$
139	"	"	"	$CH_2SO_2NMe_2$
140	"	"	"	
141	"		"	CO_2H
142	"	"	"	$CONH_2$

143	"	"	"	CN
144	"	"	"	OH
145	"	"	"	OCH_3
146	"	"	"	SO_2NH_2
147	"	"	"	SO_3H
148	"	"	"	NMe_2
149	"	"	"	$CONMe_2$
150	"	"	"	CH_2NMe_2
151	"	"	"	CH_2CN
152	"	"	"	CH_2CONH_2
153	"	"	"	CH_2CO_2H
154	"	"	"	CH_2SCH_3
155	"	"	"	CH_2SOCH_3
156	"	"	"	$CH_2SO_2CH_3$
157	"	"	"	SO_2CH_3
158	"	"	"	$SOCH_3$

159	"	"	" 
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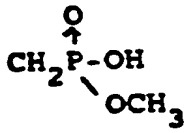
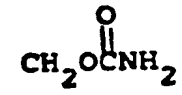
161	"	"	" CH_2SO_3H
162	"	"	" CH_2OCH_3
163	"	"	" 
164	"	"	" $CH_2CH_2SO_3H$
165	"	"	" CF_3
166	"	"	" 
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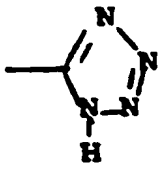
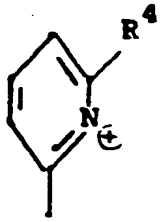
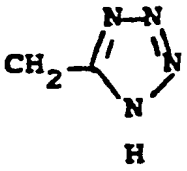
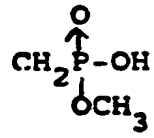
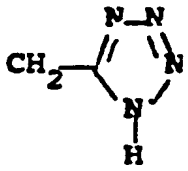
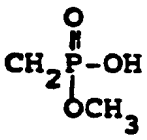
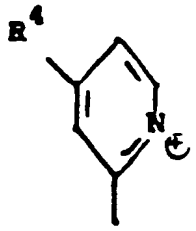
168	"	"	" $CH_2SO_2NMe_2$
169	"	"	" 

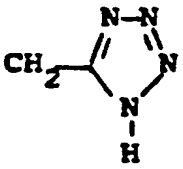
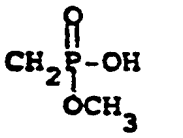
170	"	"	"	F
171	"	"	"	Cl
172	"	"	"	Br
173	"		"	CO_2H
174	"	"	"	$CONH_2$
175	"	"	"	CN
176	"	"	"	SO_2NH_2
177	"	"	"	SO_3H
178	"	"	"	NMe_2
179	"	"	"	$CONMe_2$
180	"	"	"	CH_2NMe_2
181	"	"	"	CH_2CN
182	"	"	"	CH_2CONH_2
183	"	"	"	CH_2CO_2H

184	"	"	"	CH_2SCH_3
185	"	"	"	CH_2SOCH_3
186	"	"	"	$CH_2SO_2CH_3$
187	"	"	"	SO_2CH_3
188	"	"	"	
189	"	"	"	$CH_2CH_2CO_2H$
190	"	"	"	CH_2SO_3H
191	"	"	"	CH_2OCH_3
192	"	"	"	
193	"	"	"	$CH_2CH_2SO_3H$
194	"	"	"	CF_3
195	"	"	"	CH_2OCNH_2
196	"	"	"	$CH_2SO_2NH_2$

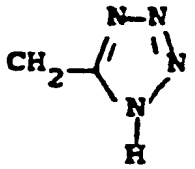
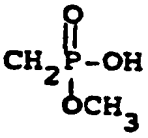
197	"		"	CO_2H
198	"	"	"	$CONH_2$
199	"	"	"	CN
200	"	"	"	OH
201	"	"	"	SO_2NH_2
202	"	"	"	SO_3H
203	"	"	"	NMe_2
204	"	"	"	$CONMe_2$
205	"	"	"	CH_2NMe_2
206	"	"	"	CH_2CN
207	"	"	"	CH_2CONH_2
208	"	"	"	CH_2CO_2H
209	"	"	"	CH_2SCH_3
210	"	"	"	CH_2SOCH_3

211	"	"	"	$CH_2SO_2CH_3$
212	"	"	"	SO_2CH_3
213	"	"	"	$SOCH_3$
214	"	"	"	
215	"	"	"	$CH_2CH_2CO_2H$
216	"	"	"	CH_2SO_3H
217	"	"	"	CH_2OCH_3
218	"	"	"	
219	"	"	"	$CH_2CH_2SO_3H$
220	"	"	"	CF_3
221	"	"	"	
222	"	"	"	$CH_2SO_2NH_2$
223	"	"	"	Br

224	"	"	"	Cl
225	"	"	"	F
226	"		"	CO_2H
227	"	"	"	$CONH_2$
228	"	"	"	CN
229	"	"	"	SO_2NH_2
230	"	"	"	SO_3H
231	"	"	"	NMe_2
232	"	"	"	$CONMe_2$
233	"	"	"	CH_2NMe_2
234	"	"	"	CH_2CN
235	"	"	"	CH_2CONH_2
236	"	"	"	CH_2CO_2H
237	"	"	"	CH_2SCH_3

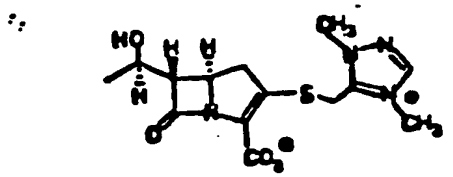
238	"	"	"	CH_2SOCH_3
239	"	"	"	$CH_2SO_2CH_3$
240	"	"	"	SO_2CH_3
241	"	"	"	$SOCH_3$
242	"	"	"	
243	"	"	"	$CH_2CH_2CO_2H$
244	"	"	"	CH_2SO_3H
245	"	"	"	CH_2OCH_3
246	"	"	"	
247	"	"	"	$CH_2CH_2SO_3H$
248	"	"	"	CF_3
249	"	"	"	$CH_2O\overset{O}{\overset{\|}{C}}NH_2$
250	"	"	"	$CH_2SO_2NH_2$

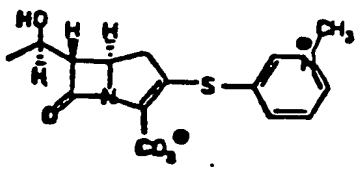
251	"		"	CO_2H
252	"	"	"	$CONH_2$
253	"	"	"	CN
254	"	"	"	OH
255	"	"	"	SO_2NH_2
256	"	"	"	SO_3H
257	"	"	"	NMe_2
258	"	"	"	$CONMe_2$
259	"	"	"	CH_2NMe_2
260	"	"	"	CH_2CN
261	"	"	"	CH_2CONH_2
262	"	"	"	CH_2CO_2H
263	"	"	"	CH_2SCH_3
264	"	"	"	CH_2SOCH_3

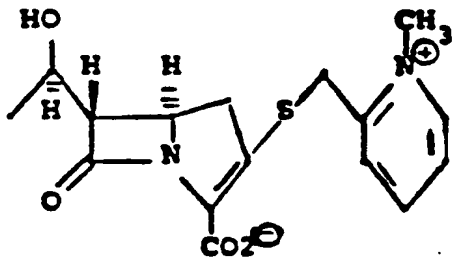
265	"	"	"	$CH_2SO_2CH_3$
266	"	"	"	SO_2CH_3
267	"	"	"	$SOCH_3$
268	"	"	"	
269	"	"	"	$CH_2CH_2CO_2H$
270	"	"	"	CH_2SO_3H
271	"	"	"	CH_2OCH_3
272	"	"	"	
273	"	"	"	$CH_2CH_2SO_3H$
274	"	"	"	CF_3
275	"	"	"	$CH_2O\overset{O}{\overset{\|}{C}}NH_2$
276	"	"	"	$CH_2SO_2NH_2$

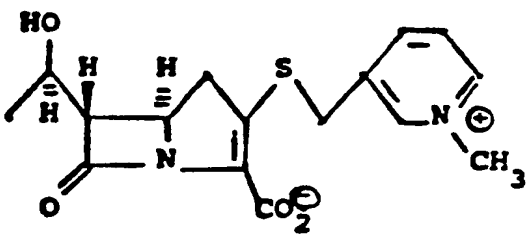
277	"	"	"	Br
278	"	"	"	Cl
279	"	"	"	F

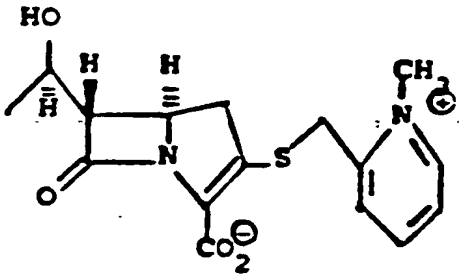
8. A compound of Claim 1 wherein the compound is a member selected from the group consisting of:

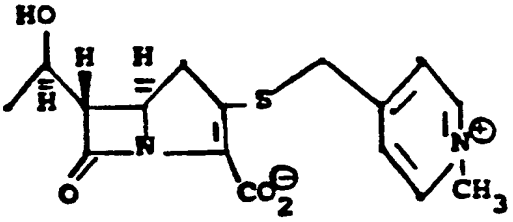


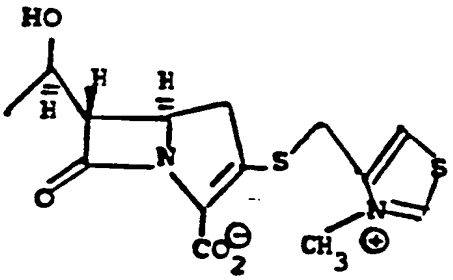


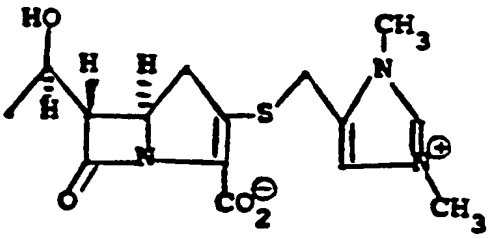


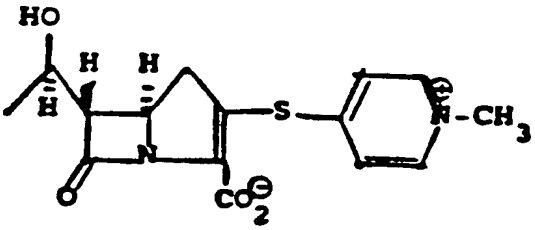


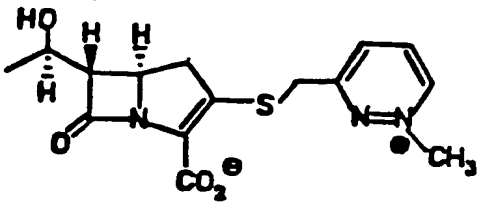












BNSDOCID: <EP___0167139A1_I_>

9. The combination of a compound of Claim 1 and a DHP inhibitor.

10. A combination of Claim 9 wherein the DHP inhibitor is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropane-carboxamide)-2-heptenoic acid.

11. A pharmaceutical composition for antibiotic use comprising an antibacterially effective amount of a compound of Claim 1, an inhibitorily effective amount of a DHP inhibitor, and, optionally, a pharmaceutically acceptable carrier.

12. A pharmaceutical composition according to Claim 11 wherein the DHP inhibitor is 7-(L-2-amino-2-carboxyethylthio)-2-(2,2-dimethylcyclopropanecarboxamide)-2-heptenoic acid.

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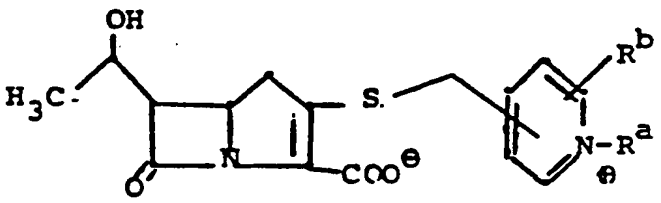
13. A compound of Claim 1 of the structure:



wherein

R^a is C_{1-4} alkyl; or an acidic sidechain of the structure $-(CH_2)_n-X-(CH_2)_m-Y-A$ where:

n = 0-4

m = 0-4

X = CHR^s, CH=CH, phenylene ($-C_6H_4-$), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, CONH, OCO_2, OC=O, NHC=O;

R^s = H, O(C1-C4 alkyl), NH_2, NH(C1-C4 alkyl), N(C1-C4 alkyl)$_2$, CN, $CONH_2$, CON(C1-C4 alkyl)$_2$, CO_2H, SO_2NH_2, SO_2NH(C1-C4 alkyl);

Y = single bond, NH, N(C1-C4 alkyl), O, S;

A = an acidic function ;

R^b is hydrogen; cyano; or an acidic side-chain of the structure -A or $-(CH_2)_n-X-(CH_2)_m-Y-A$

where

n = 0-4

m = 0-4

X = CHR^s, CH=CH, phenylene ($-C_6H_4-$), NH, N(C1-C4 alkyl), O, S, S=O, C=O, SO_2, SO_2NH, CO_2, $CONH,OCO_2$, OC=O, NHC=O;

R^s = H, O(C1-C4 alkyl), NH_2, NH(C1-C4 alkyl), $N(C1-C4\ alkyl)_2$, CN, $CONH_2$, $CON(C1-C4\ alkyl)_2$, CO_2H, SO_2NH_2, $SO_2NH(C1-C4\ alkyl)$;

Y = single bond, NH, N(C1-C4 alkyl), O, S;

A = an acidic function ;

provided that R^a or R^b must be an acidic side-chain.

14. A compound of Claim 13 wherein the acidic function -A is a member selected from the group consisting essentially of carboxy (CO_2H), phosphono [$P=O(OH)_2$], alkylphosphono [$P=O(OH)[O(C1-C4\ alkyl)]$], alkylphosphinyl [$P=O(OH)(C1-C4\ alkyl)$], substituted phosphoramido [$P=O(OH)NH(C1-C4\ alkyl)$ and $P=O(OH)NHR^x$], sulfino (SO_2H), sulfo (SO_3H), 5-tetrazolyl (CN_4H), arylsulfonamido (SO_2NHR^x) and acylsulfonamides represented by the structures $CONHSO_2(C1-C4\ alkyl)$, $CONHSO_2N(C1-C4\ alkyl)_2$ $SO_2NHCO(C1-C4\ alkyl)$ and SO_2NHCOR^x wherein R^x = aryl or heteroaryl.

15. A pharmaceutical composition for antibiotic use comprising an antibacterially effective amount of a compound of Claim 14, an inhibitorily effective amount of a DHP inhibitor, and, optionally, a pharmaceutical carrier.

European Patent Office

EUROPEAN SEARCH REPORT

0167139
Application number

DOCUMENTS CONSIDERED TO BE RELEVANT

EP 85108135.6

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	DE - A1 - 3 334 937 (BRISTOL-MYERS CO.) * Claims 1,2,4,6-8,10,12,17,167 * * Claim 167 *	1-8, 13,14 9-12, 15	C 07 D 487/04 A 61 K 31/40 C 07 D 519/00
D,Y	EP - A1 - 0 007 614 (MERCK & CO. INC.) * Claims 1,7; page 17, lines 5,6 *	9-12, 15	
D,Y	EP - A1 - 0 072 014 (MERCK & CO. INC.) * Claims 1,7,14 *	9-12, 15	
A	EP - A1 - 0 021 082 (MERCK & CO. INC.) * Claims 1,3,5 *	1-8, 11,13-15	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 487/00 A 61 K 31/00 C 07 D 519/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	25-09-1985	PETROUSEK

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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P : intermediate document

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E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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